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THE NATURAL HISTORY OF PRIMARY TUBERCULOSIS

by

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The Natural History of Primary Tuberculosis

1. Introduction

To describe the natural history of any infection it is necessary to observe a sufficient number of subjects from the time of infection through the evolution of the relationship of the infective agent and the human host until either the infective agent overcomes the host or the defences of the host contain and then eliminate the infection. With some infections these processes are rapid and a matter of days or weeks. With others such as tuberculosis or syphilis the relationship, unless altered by treatment, is prolonged and must be considered in years or even decades if the full story is to be obtained.

If the moment of infection can also pass undetected because it may not be marked by any acute change in clinical state the task is even more difficult. This is also the situation with tuberculosis. Furthermore, in describing the relationship between the invading organism and the human host it is necessary to remember that the power of the host to "resist", that is to prevent the multiplication of the invading organisms and ultimately to eliminate them is not constant throughout life but varies with many factors, three of special importance being age at infection, nutritional state and the effect of other infective conditions. Thus the evolution and outcome of the infection are influenced by many variables which must be taken into account when attempting to describe the natural history and assess the risk of damage to, or even death of, the host.

The observation that the mammalian immune process reacts in a different manner to the second invasion of the tissues with Mycobacterium tuberculosis than it does to the first was made by Koch (1891). Since then the concept of primary infection which is to be described has grown slowly as a result of the observations of many workers in different parts of the world who studied tuberculosis either in the laboratory or by clinical experience before chemotherapy became available. Outstanding in the shaping of the concepts were Gohn (1912), Ranke (1917), Rich and McCordock (1929) and Wallgren (1938 (a) and (b), 1948).

2. Paths and sites of primary infection

Pulmonary tuberculosis is the classic example of an airborne infection. When a person with open pulmonary tuberculosis coughs, especially if the cough is forcible or explosive, many droplets of different sizes containing tubercle bacilli are ejected. The smallest are invisible, evaporate almost instantly to still smaller droplet nuclei and become dispersed in the air moving as the air itself moves. If the coughing takes place in a confined and unventilated space the number of droplet nuclei increases with repeated coughing and the chance that some may be inhaled by other persons also increases. Droplet nuclei are important because they persist in the air after the infective person has left the room and owing to their size (less than 10μ) they can penetrate to the smallest bronchioles and reach the subpleural space. (Riley 1982)

Occasionally, human droplets containing bacilli may be introduced to a small wound or abrasion in the skin or on a mucous membrane and this becomes the site of a primary focus (Miller 1953). Infection has even been recorded following immersion in contaminated water (Sénécal 1950).

The spread of M. bovis is also initially by droplets expelled as the cow coughs. In this way infection may spread to the lungs of the cow-herds and the milk can become contaminated. If this milk is then consumed without pasteurisation or boiling infection may be lodged in the tonsils, in the oro-pharynx or in the alimentary tract.

3. Concept of primary infection

Wherever and whenever tubercle bacilli (M. tuberculosis or M. bovis) first lodge in the tissues of a human host the invasion initiates a sequence of events which is always the same although they may differ in degree with certain characteristics of the host, principally with age and nutrition. The events which follow are also related in time so that it is possible to describe a "time-table" (Wallgren 1948, and Figure 2).

After infection some bacilli remain at the site of entry, and others are carried in the lymph flow to the nearest lymph nodes. Bacilli then multiply in both sites and as the defense mechanism of the host comes into play, "tubercles" form so that a lesion develops at the point of entry and the regional nodes enlarge. Wherever its site, the lesion (focus) and nodes together form the primary complex. Gradually, the nodes further in the line of lymph drainage also become involved. As this occurs small numbers of organisms are disseminated in the blood stream.

Some 4-8 weeks after first infection, most people develop "sensitivity" to tuberculo-protein and the defense mechanisms accelerate. The degree of sensitivity developed varies with age and nutrition and probably with the weight of infection. The phenomenon is used in the tuberculin test to detect whether or not an individual has been infected at some time previous to the test. In most children or young adults these defense mechanisms are sufficient to contain and then slowly to heal the tuberculous process in both the focus and the nodes without the development of clinical illness. But the infection can be progressive and complications can arise from either the primary focus or the nodes if the body defenses are insufficient. The organisms disseminated in the blood stream can also form tuberculous seedings in distant organs such as brain, bones or kidney and if extension occurs in any of these sites clinical illness can result. Organisms can remain dormant both in the primary complex or in disseminated seedings and if the balance reached between organism and host is at any time tipped in favour of the former, then active tuberculous lesions may arise even years after the initial infection.

4. The evolution and healing of the primary complex

The evolution of the pulmonary primary lesion from the time of infection to healing was worked out in detail by Sweany (1941) and Medlar (1948) by the examination of primary foci of known duration in both human tissues and animals, the latter being produced experimentally.

The first response to the presence of tubercle bacilli is serous exudate and the collection of polymorphonuclear leucocytes. This is followed within 48 hours by monocytes and by mononuclear epitheloid cells of local origin the number of which steadily increase until about the end of the second week when giant cells begin to form and small numbers of lymphocytes appear. About this time the cells in the centre of the tubercle die and undergo the change known as caseation. This central area increases as the tubercle becomes larger and ultimately forms the grey-white nodule so characteristic of tuberculosis. At some time during the second month the number of lymphocytes quickly increases forming a zone around the developing tubercle. This change appears to coincide with the development of tuberculin sensitivity.

the caseous material enter the pleurae there is also the danger that a tuberculous empyema will develop. This complication usually occurs within six months of infection.

If the focus extends without rupturing into the pleural sac, it might open into a bronchus [Fig. 1.A (iii)]. If the contents are then coughed up a cavity, sometimes a tension cavity, is the result. Except occasionally in infants cavitation was uncommon in European countries between 1930 and 1960 but still occurs in children of all ages in countries of Africa and South-East Asia. It may also be the beginning of spread to other parts of the lung and part of the mechanism of spread which causes the extensive pulmonary involvement so common in malnourished children in Africa (Carter 1954). Like pleural effusion this type of cavitation tends to occur within a few months of infection [Fig. 2].

Sometimes the primary focus remains almost unchanged in periods of equilibrium with the host's powers of resistance, or periods of extension and periods of healing may alternate so that the focus comes to have a laminated appearance. Such a round shadow (coin or numular shadow) can persist for many months until it is calcified, or opening into a bronchus, the caseous material is coughed up and the radiological shadow disappears [Fig. 1.A (iv)].

6.2 The regional nodes

When the primary focus is in a lung the regional nodes draining it are situated at the junction of the bronchi supplying the same pulmonary segment, and at the broncho-pulmonary nodes at the root of the lung. These in turn drain into paratracheal nodes. These nodes enlarge as their contents become caseous and may soften to form what amounts to an abscess. As the nodes lie in relation to both bronchi and to blood vessels either structure can be eroded by the tuberculous process or, in very young children, the bronchi may be compressed. When a bronchus becomes eroded by tuberculous endobronchitis the contents of the nodes may leak or be extruded into the lumen. When this does happen the result depends upon the physical state of the caseous material and the number of viable organisms it contains. The possibilities are shown in Figure 1.B (i-iv). The extent of lung involved depends on the order of the bronchus eroded - whether segmented, lobar or that involving a whole lung.

(i) Hyperinflation. When the bronchi is partly but incompletely obstructed so that during inspiration some air can pass into the lung beyond, but on expiration the obstruction is complete, the segment of lung beyond the block becomes over distended [Fig. 1.B (i)]. This ball-valve obstruction can affect a segment, a lobe or a complete lung. This situation by its very nature is unstable and transient and the bronchus either blocks completely or the material is coughed up.

(ii) Collapse. If complete obstruction occurs and the air beyond is absorbed then the lung distal to the obstruction collapses as the pressure falls [Fig. 1.B (ii)].

(iii) Collapse-consolidation. More usual than either over-inflation or complete absorption-collapse is the situation when some of the contents of the node have leaked into the bronchus and are inhaled further into the lung beyond. The contents contain tuberculin and varying numbers of bacilli and set up an inflammatory reaction in the distal lung - the two extremes of reaction are first a non-specific exudation with few if any tubercles [Fig. 1.B (iii)] or secondly, the beginning of a progressive tuberculous broncho-pneumonia [Fig. 1.B (iv)]. The first of these two

extremes is the most common type of segmental lesion formerly seen in Europe whilst the second appears to be a stage in the development of the progressive pulmonary tuberculosis of African children [Fig. 1.B (iv)].

The segmental consolidations may leave permanent structural changes in the affected lobe or segment of lung and its bronchi. These changes shown diagrammatically in Fig. 1.C (i-iv) are:

(i) Bronchial stricture by scarring at the point where the wall of the bronchus was eroded by the tuberculous node.

(ii) Cylindrical bronchiectasis in the shrunken lobe or segment which failed to reexpand after bronchial obstruction.

(iii) Bronchiectasis in a shrunken lobe or segment which has been the site of consolidation and then slow healing by fibrosis and contracture.

(iv) Sometimes the healed fibrotic area may appear simply as linear scarring on an X-ray film.

Segmental lesions occur most frequently between three and nine months after primary infection and can remain as radiological shadows for months without any noticeable change in the child's condition. If, however, the number of bacilli is sufficient to overcome resistance then, as already stated, progressive tuberculous broncho-pneumonia is the result.

Caseous nodes about the carina can also ulcerate forwards and leak or rupture through the posterior wall of the pericardium into the pericardial sac and there set up a pericarditis which may be serous [Fig. 1.C (v)] or adherent obliterating the cavity. Posteriorly the oesophagus can be involved and the contents of the node discharged into its lumen and later if an adherent scar remains it may be the beginning of an oesophageal pouch.

6.3 Haematagenous dissemination

During the formation of the primary complex and for some time afterwards bacilli escape intermittantly into the blood stream and are carried to other parts of the body. There is good evidence that this can happen without the development of clinical illness. Thus choroidal tubercles were seen in six of one hundred consecutive children with asymptomatic primary infections. Monbrun and Lavat (1949) and Webster (1942) and Munro (1944) recorded the intermittent discharge of bacilli in the urine without any symptoms of renal disease. Tubercles have also been found in the livers of persons accidently killed following a recent primary infection.

Although this intermittent spread does produce scattered seedings the important point is whether any of these small lesions continue to enlarge and damage tissue as in bone disease or by rupturing into a cavity cause widespread reaction as occurs when a subcortical lesion in the brain (Rich focus) leaks into the subarachnoid space and tuberculous meningitis follows.

Blood spread can also take place within the lungs and probably occurs both through the pulmonary veins and general circulation or by local spread through small vessels. Small tubercles known as Simon foci appear particularly at the apices (Simon 1943). It is possible that after a long interval these foci might sometimes again become active and give rise to chronic pulmonary lesions.

of the radiological findings, 93 of the children had evidence of an old primary complex in the same segment or lobe as the recent progressive disease. The same situation must arise in adolescents.

Further evidence also pointing to the reactivation of primary pulmonary lesions (endogenous exacerbation) was found in long-term BCG trials in populations in America and the United Kingdom. During these studies, over the years when the risk of infection was steadily falling, the incidence of active pulmonary tuberculosis in the infected unvaccinated group was greater than in either the unvaccinated uninfected or the vaccinated group (Medical Research Council, 1963, 1977; Ferebee and Palmer, 1965).

In countries where pulmonary tuberculosis is prevalent in adults and the risk of infection is high many cases of pulmonary tuberculosis must be caused by exogenous reinfection in persons who have previously had a primary infection. Thus the total morbidity of pulmonary tuberculosis in adults in any community comprises three components, endogenous exacerbation of former primary infections, the progressive primary infections of adult life and exogenous reinfection in persons who have healed a previous primary infection. The proportion which each of these contributes to the total morbidity from pulmonary tuberculosis varies from community to community and the annual risk of infection in each. As this risk declines the proportion of cases due to endogenous exacerbation will increase.

9. Extrapulmonary primary infection [Fig. 3]

The distribution of 66 extra pulmonary lesions all seen in the course of clinical work with children in the North-East of England between 1948 and 1960 is shown in Figure 3. The sites of primary infection were in the conjunctiva, on the face and forehead, in the mouth and oro-pharynx, on the forearms and knees, legs and feet. These are sites which, in children, are often subject to minor trauma and also to contamination by dust or fluids which might contain tubercle bacilli or to droplet infection from adults.

Milk was previously a common source of infection and still is in certain areas. The infecting organism is then either *M. bovis* or, by human contamination *M. tuberculosis*, and the primary lesion is in the tonsil or the oro-pharynx, or the intestine or in both. But other foods, cutlery or dental instruments contaminated by *M. tuberculosis* can produce lesions in the same sites.

Except when the primary focus is in the intestine the clue to its position is given by the site of the group of enlarged superficial regional nodes of the complex. The lymph drainage from the lesion is accurate so the lesion must be sought in the area drained by the nodes involved. Any small ulcer or scab in the area should be suspected and investigated. In this way, the origin of superficial tuberculosis lymphadenitis is explained and fits into the picture of primary infection (Miller 1953, Miller and Cashman, 1958).

Most regional nodes enlarge slowly and painlessly but occasionally the onset may be swift with high fever and much perinodal oedema so that the individual nodes cannot be recognized. Whatever the type of onset most nodes sooner or later soften to form superficial abscesses which may be drained or discharged. However, calcification can occur and then the node may remain dormant for many years before finally softening.

Whilst the primary lesion is forming, bacilli escape into the blood stream and are seeded just as in pulmonary primary lesions so that the risk of haematogenous lesions exists wherever the primary complex forms.

For intestinal primary infection, the regional nodes are deep in the mesentery and their presence can only be suspected if they cause an omental roll, adhesions between loops of gut or, rupturing, an effusion with abdominal swelling. The mesenteric nodes, like others, may calcify and remain dormant for years.

10. Conclusion

In this short description of the evolution and natural history of primary tuberculosis infection, an attempt has been made to view tuberculosis as a general disease and to relate all its manifestations in time and in relation to the age and nutrition of the human host. It is in fact a plea that the relationship of the tubercle bacillus and the human host can only be understood if it is seen to begin with the primary infection or first invasion of the host and if it is regarded as a general disease and not as a medical, surgical or dermatological problem depending upon the hospital department or the 'specialist' which the patient happens to reach.

Table 1 Incidence (per cent) of complications of untreated primary tuberculous infection at different ages

Age at infection (years)	Author	Number observed	Source	% Meningitis and miliary	Pleural effusion	Segmental lesion	Skeletal	Pulmonary tuberculosis
0–2	Payne (1959) England	69	Asymptomatic converter	16	0	23	5.7	—
0–2	Myers (1940) America	209	Routine test	4.8	—	—	—	—
0–5	Payne (1959) England	114	Asymptomatic converters	2.6	2.6	11.4	0.9	—
0–5	Davies (1961) London	74	Observation at contact clinic	2.6	—	5	1.3	—
0–5	Cammock & Miller (1953) England	1020	Estimated converters	3.5	—	—	1.5	—
0–5	Lotte & Rouillon (1960) France	314	Asymptomatic converters	3	1.9	3.5	—	—
0–7	Holmdahl (1950) Sweden	657	Erythema nodosum	3.8	12.7	—	—	9.2
0–7	Miller et al (1960) England	99	Routine testing in longitudinal survey	6	0	23	3	—

— Not recorded or not applicable.

Table 2 Polarization of manifestations of tuberculosis

Manifestation	'Temperate'	'Tropical'
Size of primary infection	+	++
Amount of caseation	+	++
Size of regional nodes	+	++
Sensitivity phenomenon		
Erythema nodosum	+++	+
Phlyctenular conjunctivitis	+++	+
Pleural effusion	++	+
Abdominal ascites	++	+
Tuberculosis of central nervous system (including tuberculomata)	+	+++
Degree of skin sensitivity	+++	+
Frequency of multiple lesions	+	++
Frequency of primary cavitation	+	++

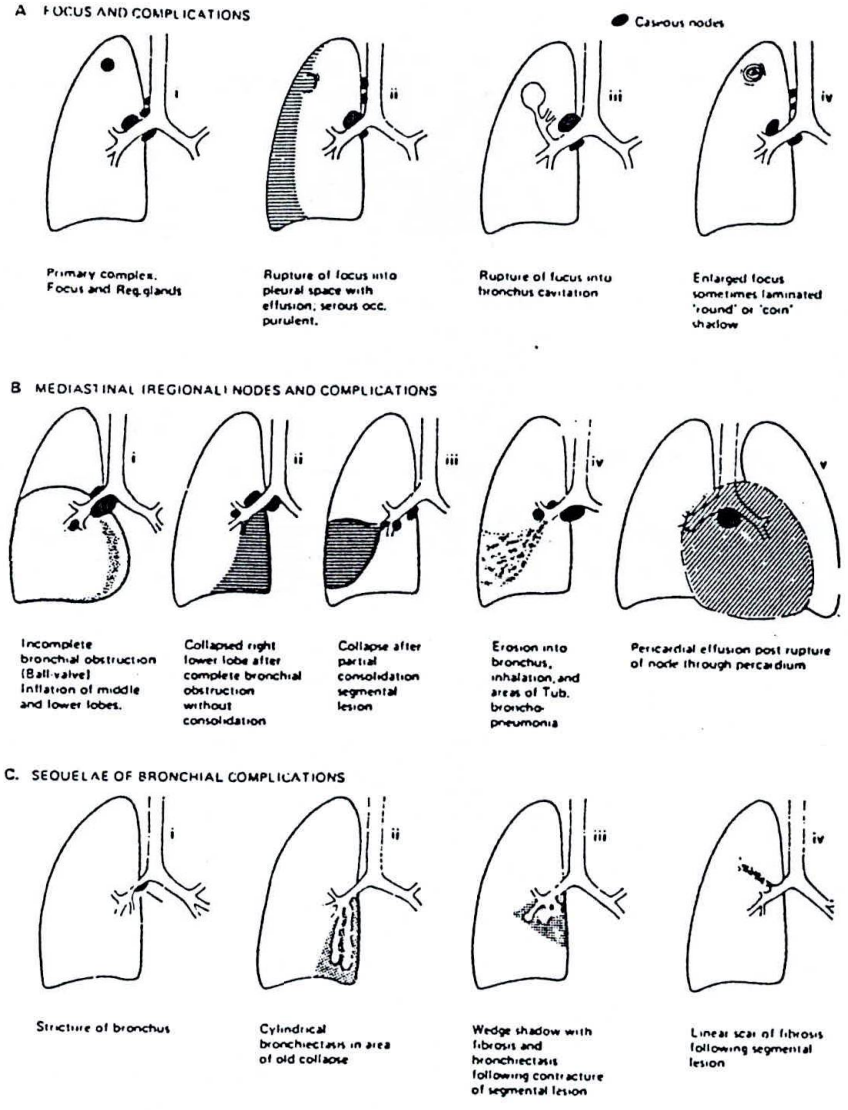

Fig. 1 The complications and sequelae of Pulmonary primary tuberculous infection

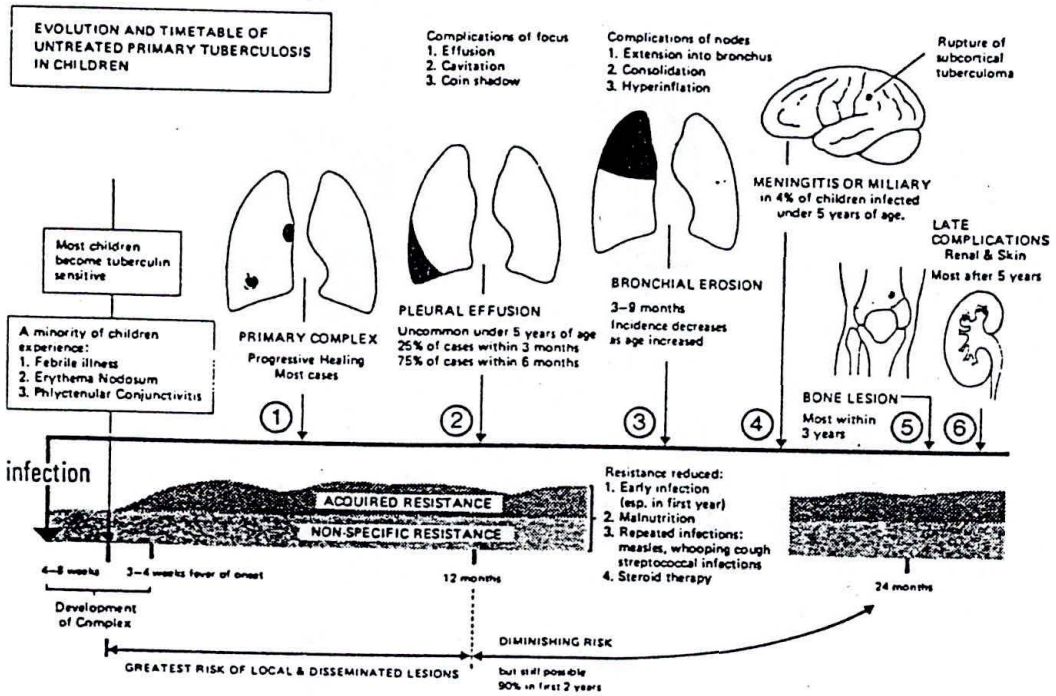

Fig. 2 Evolution and Timetable of untreated primary tuberculous infection

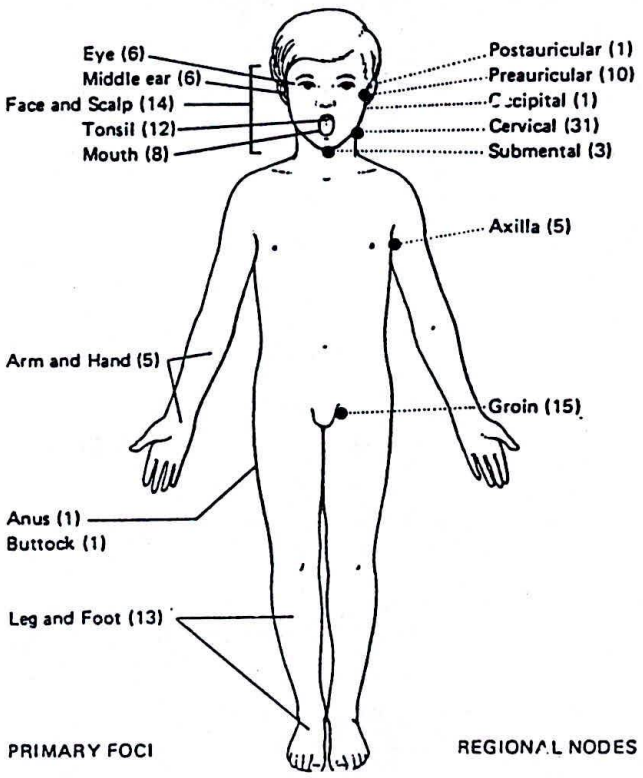

Fig. 3 Distribution of primary foci and regional nodes in 66 children with primary infection on skin or mucous membranes

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Terminology

Primary focus:

A primary focus is the cellular and structural change occurring in response to the presence and multiplication of M. tuberculosis (or M. bovis) at the site of first implantation into the tissues of the host: the usual site for M. tuberculosis is in a lung and for M. bovis in the oro-pharynx or intestinal tract.

Primary complex:

The primary focus and associated lymphadenitis.

Tubercle:

When M. tuberculosis or M. bovis invades human tissue the first visible response is by polymorphonuclear cells. Then, within 48 hours monocytes and epitheloid cells appear and increase in numbers. Within about 7 days some lymphocytes can be seen but, unless the body has been previously sensitised to tuberculin large numbers do not appear until the second month. Meanwhile from the third week giant cells begin to form.

This aggregation of cells is the basic lesion of tuberculosis and is known as a tubercle.

Caseation:

From about the 10-14 day after infection the cells in the central part of the developing tubercle begin to lose their outlines and become amorphous. This death of cells is a reflection of the relationship between the local multiplication of organisms and the resistance of the host but the central area of caseation is part of the tubercle. The caseous area can continue to enlarge and may merge with that of other tubercles if the pathological process extends.

The caseous material is grey-white in colour and it is this which gives the macroscopic tubercle its characteristic appearance.

Exogenous reinfection:

The production of a tuberculous lesion by a new infection, from another source outside the body in a person who has had a primary infection and has remained tuberculin sensitive.

Endogenous exacerbation:

The reactivation of an old and apparently healed tuberculous lesion derived from the primary focus, the associated adenitis or the haematogenous seedings thereof. The term endogenous reinfection is sometimes used to describe the same process.

Segmental lesion:

The involvement of a pulmonary segment, lobe or whole lung secondary to bronchial erosion with the aspiration of material from the affected nodes. The term is descriptive of the extent of pulmonary involvement and does not denote the histological changes in the affected area.

Hyperinflation (sometimes called obstructive emphysema):

The hyperinflation of a pulmonary segment, lobe or whole lung resulting from incomplete bronchial obstruction having a ball-valve effect allowing air to enter but not to leave the affected segment or lobe.

Tension cavity:

If a caseous lesion opens into a bronchus the contents may be coughed up and a cavity results; sometimes the communication between cavity and bronchus will allow air to enter on inspiration but impedes the flow during expiration. These cavities radiologically appear to be thin walled and translucent and may quickly disappear with treatment.

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STATE OF THE ART

I. – EPIDEMIOLOGY OF TUBERCULOSIS

K. Styblo*

The main aim of this paper is to summarise, in a simple way, recent studies on the epidemiology of tuberculosis to give us a better understanding of the way in which tuberculosis behaves and maintains itself in the community. These studies are also relevant to the planning of programmes for tuberculosis control in developing countries and for eradication of the disease in developed ones.

The following items will be discussed:

1) The natural interactions between the tubercle bacillus and a human population.
2) Epidemiological indices for evaluation of the overall tuberculosis situation and its trend.
3) The so-called «natural» trend of tuberculosis in developed and developing countries.
4) Impact of present control measures on the tuberculosis situation.
5) Recent, present and future situation of tuberculosis in developed and developing countries.
6) Use of the two basic tools for planning an efficient tuberculosis programme in developing countries and eradication of tuberculosis in developed countries.

In the present paper only the first two items will be considered. The remaining four will be dealt with by Dr. J. Meijer and myself at the World Conference of the IUAT to be held in Brussels in September 1978.

In order to make the present paper easier to understand and more readable, I have tried to keep it as short as possible. More detailed information on some topics of the paper is given in the appendices. A comprehensive study «Recent advances in epidemiological research» will shortly be published in «Advances in Tuberculosis Research» (1).

1. *Natural Interactions between the Tubercle Bacillus and a Human Population*

The natural interactions between the tubercle bacillus and a human population can only be studied if there is no man-made interference. Therefore, post-war routine statistics from developed countries cannot be used for studying this subject, as there has been uninterrupted interference, especially from chemotherapy, which has influenced one or more parameters.**

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** A parameter is defined as a «constant» indicating the numerical value which links two variables (see below) together. Parameters are constant under natural conditions only, i.e. without man-made interference. They may depend to some extent upon socio-economic conditions.

Examples of parameters: a «contagious» parameter refers to the average number of persons infected with tubercle bacilli during one year by one source of infection. The disease ratio expresses the proportion of cases in which infection with tubercle bacilli leads to the development of a source of infection.

N.B. The other expression to be clarified is the term «variable». Such quantities are not constant but vary with time in a given population and among various population groups. Two important variables in tuberculosis epidemiology are prevalence and incidence.

An extensive study of *morbidity* in contacts (more than 8,000 intimate and 11,000 casual contacts) was recently carried out in British Columbia and Saskatchewan (Canada) (7). Tuberculosis was rare in intimate contacts of culture-negative sources, and no cases of tuberculosis were observed among casual contacts of culture-negative sources. Disease rates were also substantially lower (0.8% for whites and 2.3% for Indians) among intimate contacts of culture-positive cases than among intimate contacts of smear-positive sources (5.9% and 8.2% respectively).

These observations confirm once more that *the bacillary status of the patient decides the extent to which he can transmit tubercle bacilli to other hosts.* For the purpose of this study, patients with smear-positive tuberculosis will be considered as sources of infection, and other patients will not.

(iii) *The «contagious» parameter* is computed as:

$$\frac{\text{annual tuberculosis infection rate (\%)}}{\text{prevalence of sources of infection (per 100,000)}} \times 1000$$

Some estimates of the «contagious» parameter are given in Appendix II.

Our best estimate is that *about 10 persons are infected, on average, with tubercle bacilli during one year by one unknown smear-positive case of pulmonary tuberculosis.*

1.2 DEVELOPMENT OF INFECTIOUS TUBERCULOSIS FOLLOWING INFECTION WITH TUBERCLE BACILLI

The risk resulting from tuberculous infection is greater for persons not previously infected than for those who have been previously infected with virulent tubercle bacilli. We shall refer to the disease following primary infection as «primary» tuberculosis. The disease which occurs in those previously infected with tubercle bacilli will, for our purpose, be called «secondary» tuberculosis*. In epidemiological studies it is necessary to adopt a precise working distinction between «primary» and «secondary» pulmonary tuberculosis. Dr. Holm has suggested the following:

(a) Any pulmonary tuberculosis developing and being diagnosed during the first five years following primary infection is classified as «primary» tuberculosis.
(b) Any pulmonary tuberculosis diagnosed more than five years after primary infection is classified as «secondary» tuberculosis.

(a) *«Primary» Tuberculosis*

If the annual tuberculosis infection rate is high, as it was in developed countries before World War II and still is in many developing countries at present, «primary» tuberculosis occurs mostly among children. If the risk of infection is low, a low rate of «primary» tuberculosis will occur among children as well as adults.

Extensive information on the bacteriological status of children suffering from «primary» tuberculosis is available in many developed countries where BCG vaccination has not been practised. All the statistics show that *few* children with «primary» tuberculosis develop bacillary pulmonary tuberculosis (in Norway 2.6%; in Denmark 4.9%; in The Netherlands 0.9% – based on cases reported during the period 1951-1968); and *very few* children develop *smear-positive* (infectious) tuberculosis which is considered to be the most important source of infection.

However, much less is known about the development of the disease, and especially its bacteriological status, if the primary infection occurs during adolescence. As regards higher age-groups, very little is known.

Information from X-ray and tuberculin surveys carried out in Saskatchewan since 1955 made it possible to study the breakdown risk in persons who acquired primary infection during adolescence and

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* This nomenclature is used for brevity's sake. The terms «primary» and «secondary» tuberculosis have no clinical meaning here.

the programme should be primarily focused on decreasing the *sources of infection* (case-finding and treatment).

The fundamental problem of the endogenous or exogenous origin of secondary tuberculosis, based on anatomical studies made between 1930 and 1950, and the frequency of primary resistance to drugs of *M. tuberculosis* in adults which was observed in the 1960s, has been ably reviewed by Canetti (14). Recent TSRU studies have now provided some statistical evidence on the relative importance of endogenous reactivation and exogenous re-infection for secondary tuberculosis. Reference is made to Sutherland's review (3).

We have also collected some direct evidence on the role of endogenous exacerbation and exogenous re-infection (Appendix III).

On the basis of the anatomical, bacteriological, statistical and epidemiological studies there is reliable evidence that *exogenous re-infection does play a role in the pathogenesis of bacillary pulmonary tuberculosis.* However, the role of exogenous re-infection becomes evident only if the tuberculosis infection rate is high.

1.3 THE FATE OF THOSE SUFFERING FROM INFECTIOUS TUBERCULOSIS

It is of great epidemiological interest to know the natural history of infectious pulmonary tuberculosis, i.e. the chances of recovery and death from the disease in the absence of chemotherapy. There is an expression for this in the lethality, by which is meant that proportion of the number of notified patients who die of pulmonary tuberculosis.

Data referring to the fate of cases not given chemotherapy were obtained from several sources. M. Lindhart (20) studied the occurrence of pulmonary tuberculosis in Denmark during the period 1925-1934 and its lethality during an observation period of 8 years. A total of 17,189 men and 22,190 women were notified as having pulmonary tuberculosis (bacillary and non-bacillary) during the period under study. She produced a simple survival table, for males and females separately (Table 1). By placing the «survivors» (i.e. those who had not died of pulmonary tuberculosis) in relation to those who had died in the 2nd, 3rd, 4th, etc. years of observation, she arrived at the lethality percentages. Putting the original total of notified cases at 1000, as in an ordinary life table, and by means of the lethality percentage, and calculating how many of these were left after the 2nd, 3rd, etc. observation years, she obtained the survival rate.

According to this table, after the expiry of the 8th year after notification, over half of the cases did *not* die from pulmonary tuberculosis. It must be stressed, however, that the study refers to both bacteriologically confirmed and unconfirmed cases together for all ages. For *open* (bacteriologically confirmed) cases the lethality was higher than that given in Table 1, namely about 65% for men and 66% for women at 4 years of follow-up.

Springett in Great Britain recorded the fate of 571 cases of bacillary pulmonary tuberculosis notified in the pre-chemotherapy period (before 1947) (21). After the expiry of the 4th year after notification 55% of the patients were dead, 26% were «cured» and the remaining 19% were still excreting tubercle bacilli.

Rutledge and Crouch (22) analysed the fate of 1,229 sputum-positive patients admitted to a sanatorium in the United States and found that 66% were dead at 4 years.

In India, a longitudinal study was conducted in the 1960s in order to observe the natural history of pulmonary tuberculosis under the socio-economic conditions existing in an area that was not yet benefitting from any of the active control measures – such as BCG vaccination and chemotherapy (23). Of the 178 bacteriologically confirmed cases found at the first survey, 126 could be followed up at three subsequent surveys carried out over the five following years. At the end of the 5-year period, 49% were dead, 33% were «cured» and 18% remained sputum-positive.

Thus, one can conclude that about *two-thirds of the patients suffering from smear-positive tuberculosis will die* from tuberculosis, in the absence of chemotherapy, during 4-5 years after the diagnosis of the disease.

2. *Epidemiological Indices for Evaluation of the Overall Tuberculosis Situation*

Two epidemiological indices are currently considered the most relevant for assessing the tuberculosis problem and its trend in a given community:

The incidence of tuberculous patients excreting tubercle bacilli demonstrable by direct smear examination.

The annual tuberculosis infection rate (the risk of tuberculous infection).

2.1 THE INCIDENCE OF TUBERCULOUS PATIENTS EXCRETING TUBERCLE BACILLI DEMONSTRABLE BY DIRECT SMEAR EXAMINATION

Theoretically, the incidence of tuberculous patients excreting tubercle bacilli demonstrable by direct smear examination is a good epidemiological index which reflects the magnitude of the tuberculosis problem in a given community, and if observed over several consecutive years it also shows the trend in the tuberculosis problem. However, its reliability is limited, to a larger or smaller extent, by several factors:

- The incidence rate is closely related to the quality and extent of case-finding activities and bacriological examination.
- A number of cases are never notified either through error or because the disease may have healed spontaneously without any medical interference.
- The calendar trend in the total incidence of smear-positive cases is an underestimate of the trend of the recent tuberculous disease, because in middle-aged and elderly persons cases keep appearing due to endogenous exacerbation.
- When the incidence in a country becomes low, the index may be unreliable because it is based on very small numbers.

In fact, the first current epidemiological index – the incidence of tuberculous patients excreting tubercle bacilli demonstrable by direct smear examination – is not used at present in most *developed* countries. The currently reported notification data in most developed countries are particularly deficient in bacteriological examination, as they do not report whether patients are smear-positive and/or culture-positive, or even whether such an examination has been performed (24).

On the other hand, most of the *developing* countries have been trying to follow the WHO recommendation and focus attention on smear-positive cases of pulmonary tuberculosis. However, in nearly all developing countries there is still a large and varying proportion of undiagnosed cases, so that notification data on the number of new smear-positive cases give inadequate information on the tuberculosis situation and its trend.

2.2 THE ANNUAL TUBERCULOSIS INFECTION RATE (THE RISK OF TUBERCULOUS INFECTION)

There is now general agreement that the annual tuberculosis infection rate is the best single indicator for evaluating the tuberculosis problem and its trend in developed and developing countries. It is an index which expresses the attacking force of tuberculosis within the community and, unlike mortality and notification rates, is *independent* of the procedures and of the intensity of the tuberculosis programme.

To obtain reliable estimates of the annual tuberculosis infection rates and *changes* in a particular period, several tuberculin surveys are required at intervals, each in a representative sample of non-BCG-vaccinated subjects of the same age, tested by the same technique.

The advantage of summarising the tuberculosis position in a country in terms of tuberculosis infection rates in particular years is that these rates provide a readily intelligible measure of the impact of tuberculosis on the community at different times. This approach also facilitates comparisons of the tuberculosis situation in different countries. Moreover, knowledge of the trend of annual tuberculosis infection rates enables comprehensive predictions to be made, both of the prevalence of tuberculous infection and of the expected incidence of tuberculosis in the population at different ages. This provides guidance on the likely magnitude of the tuberculosis problem in a country during the following ten to fifteen years.

In developing countries, where the risk of infection is still high, a relatively small sample of children would suffice for the estimation of the tuberculosis infection rate, of the order of 3,000 to 4,000 children aged about 10 years. Care should be taken to exclude from the sample children who have already had BCG vaccination.

However, in countries where the prevalence of tuberculous infection is low, and has been decreasing rapidly, it will be necessary to test many more unvaccinated children with BCG, e.g. 15,000 to 20,000 aged 15 years. A simple method of survey would be to pick a sufficient number of schools at random and test all children in these schools in the chosen age-group every five years. The most convenient approach would be to test about one-fifth of the selected schools each year, so that about 800 children would be tested each year in a developing country, and about 3,000 to 4,000 each year in a developed country.

One considerable problem in interpreting the results of a tuberculin survey is how to assess what constitutes tuberculous infection and what constitutes other mycobacterial infection in countries where the latter infection is present. Methods have been developed which allow, to some extent, separation and estimation of that proportion of the population infected with virulent tubercle bacilli.

In countries where BCG vaccination has been obligatory at birth for more than 10 years, the level of tuberculin sensitivity in young children provides no guide to the risk of infection, because sensitivity following natural infection cannot be separated from sensitivity following BCG vaccination. The only way of overcoming this difficulty is to select a representative sample of new-born children, to defer BCG vaccination of this group for (say) six years, and to assess the development of tuberculin sensitivity during this period in this unvaccinated group. Arrangements for chemoprophylaxis for any of the group who acquired a tuberculous infection would ensure that the above procedure was ethically acceptable.

* * *

The topics under 3 to 6 of this paper will be presented at the World Conference of the IUAT, in Brussels, Belgium, in September 1978.

Table 1

SURVIVAL TABLE FOR CONSUMPTIVES IN RESPECT OF DEATHS FROM PULMONARY TUBERCULOSIS. 1925-1934.

Average period of observation (years)	Males					Females				
	Total notified cases	Of which died of 1000 notified				Total notified cases	Of which died of 1000 notified			
		Total		Survived	Died		Total		Survived	Died
		No.	%				No.	%		
0.5	17,189	5124	29.8	1000	298	22,190	6635	29.9	1000	299
1.5	12,065	1142	9.4	702	66	15,555	1658	10.7	701	75
2.5	10,923	543	5.0	636	32	13,897	787	5.7	626	36
3.5	10,380	350	3.4	604	21	13,110	460	3.5	591	21
4.5	10,030	237	2.4	583	14	12,650	295	2.3	570	13
5.5	9,793	131	1.3	569	7	12,355	161	1.3	557	7
6.5	9,662	93	1.0	562	6	12,194	107	0.9	550	5
7.5	9,569	72	0.8	556	4	12,087	53	0.4	545	2

Source of information: Lindhardt, Marie: The statistics of pulmonary tuberculosis in Denmark, 1925-1934. A statistical investigation on the occurrence of pulmonary tuberculosis in the period 1925-1934, worked out on the basis of the Danish National Health Service file of notified cases and of deaths. Ejnar Munksgaard, Copenhagen 1939 (p. 100).

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Appendix I

HOW TO ESTIMATE THE ANNUAL TUBERCULOSIS INFECTION RATES

There are two steps in assessing the annual tuberculosis infection rates:

a) Estimation of the percentage decrease in the annual risk of infection using Appendix Table C of TSRU Report No. 1 (2).

Appendix Table 1 shows a part of this table. The percentage decrease in the annual tuberculosis infection rates can be estimated if two or more prevalence figures are available for subjects of the same age. If the prevalence of infection in children aged, say, 10 years was, for instance, 14.0% in 1972, and 11.0% in 1977, entry 26 in the table is divided by 5 (the interval in years between the later (1977) and the earlier (1972) surveys) to give the approximate annual percentage decrease, which is about 5% in this case. The approximate annual percentage decrease is needed for use in Appendix Table B of TSRU (2).

Appendix Table 1

Decrease in infection risk corresponding to various percentages infected by the same age at two different surveys (from TSRU (2), Appendix Table C, p. 104)

Percentage of persons already infected at the time of		the *later* survey								
		6.5	7.0	7.5	8.0	9.0	10.0	11.0	12.0	....
the *earlier* survey	7.0	8								
	7.5	15	7							
	8.0	22	14	7						
	9.0	34	26	19	12					
	10.0	45	37	30	23	11				
	11.0	55	47	40	33	21	10			
	12.0	64	57	49	43	30	19	9		
	13.0	73	65	58	51	39	28	18	9	
	14.0	81	73	66	59	47	36	*26*	17	8
	etc.									

Divide the entry in the table by the interval in years between the surveys to obtain the approximate annual percentage decrease for use in Appendix Table B.

b) Using the estimate of the percentage decrease, Appendix Table B of the same report provides direct assessments of the risk of tuberculous infection in two calendar years, namely the year in which the prevalence of tuberculous infection was determined, and a few years earlier (Appendix Table 2). In the above-mentioned case one consults Appendix Table B for children aged 10 years, 3rd column (5% annual decrease in risk of infection each year). The Table indicates the following annual tuberculosis infection rates:

1972: 1.09% (and in 1962: 1.78%)
1977: 0.84% (and in 1967: 1.38%)

Appendix Table 2

Annual percentage risks of tuberculous infection corresponding to the percentage already infected by the age of 10.5 years (from TSRU (2), Appendix Table B, p. 92)

Percentage already infected	Approximate percentage decrease in risk of infection each year						
	1		3		5		7 ... 13
	Risk this year	Risk 10 years ago	Risk this year	Risk 10 years ago	Risk this year	Risk 10 years ago	etc.
1.0	0.09	0.10	0.08	0.11	0.07	0.12	
1.5	0.14	0.15	0.12	0.16	0.11	0.18	
etc.							
11.0	1.05	1.16	0.94	1.27	*0.84*	*1.38*	
12.0	1.15	1.27	1.03	1.39	0.92	1.51	
13.0	1.25	1.38	1.12	1.51	1.00	1.65	
14.0	1.35	1.49	1.21	1.64	*1.09*	*1.78*	
etc.							

Source of information: Bleiker, M.A.: Epidemiological trends in low prevalence countries, Bull. Un. Int. Tuberc. *49*, 128-135, 1974.

Appendix II

SOME ESTIMATES OF THE «CONTAGIOUS» PARAMETER

The relationship between the annual tuberculosis infection rates and mortality rates from the pre-chemotherapy period in The Netherlands is shown in Appendix Table 3.

Appendix Table 3

Relationship between the annual tuberculosis infection rates and mortality from tuberculosis (all forms) (from Styblo, 1)

Year	The annual tuberculosis infection rate (1)	Death rate from tuberculosis (all forms)* per 10.000 (2)	(1) / (2) Infections per death (3)	(3) / (4)** Infections per source of infection (4)
1922	602	11.5	52.3	13.1
1925	513	10.0	51.3	12.8
1928	437	8.8	49.7	12.4
1931	372	7.1	52.4	13.1
1934	316	5.6	56.4	14.1
1937	269	4.8	56.0	14.0
1921-1938	.	.	53.0	13.2

* Average for 1921-1923, 1924-1926, ... 1936-1938.
** Ratio Mortality: Prevalence of Smear-positive cases = 1:4 (see text).

The annual tuberculosis infection rate was 602 per 10,000 in 1922 and decreased to 269 per 10,000 in 1937. The average death rate from tuberculosis (all forms) per 10,000 was 11.5 for 1921-1923, and gradually decreased to 4.8 for 1936-1938. The third column of Appendix Table 1 gives the proportions between the annual tuberculosis infection rates and death rates from tuberculosis from 1922, 1925, ... 1937, ranging from 49.7 to 56.4. In order to obtain estimates for the «contagious» parameter concerning prevalence (and not mortality), estimates related to mortality rates (column 3 of Appendix Table 3) were divided by four, as mortality from tuberculosis was assumed to be one-quarter of the prevalence of smear-positive cases. The estimates derived from mortality (the last column of Appendix Table 3) indicate that about 13 persons (ranging between 12 and 14) were infected with tuberculosis during one year by one source of infection in the Dutch community in the period 1921-1938.

The «contagious» parameter may depend, to some extent, on various socio-economic conditions; one should therefore attempt to obtain values for different populations. Sutherland and Fayers (10) calculated annual tuberculosis infection rates for Lesotho and Uganda. The annual infection rates at age 10 years, applied in 1960, were 410 per 10,000 for Lesotho and 220 per 10,000 for Uganda. These rates were related to the prevalences of smear-positive cases of pulmonary tuberculosis observed in the original WHO surveys carried out in Lesotho in 1957 and Uganda in 1958. It was estimated that about 14 persons in Lesotho and 10 persons in Uganda were infected with tuberculosis by one source of infection (1).

Appendix III

SOME DIRECT EVIDENCE ON THE ROLE OF ENDOGENOUS EXACERBATION AND EXOGENOUS RE-INFECTION

1) The present very low risk of tuberculous infection in a number of developed countries enables us to measure the effect of *endogenous exacerbation*, provided that the tuberculin status of the population is known before the development of bacillary tuberculosis.

A large and representative segment of the Danish population, a total of over 626,000 persons aged 15-44 years, was examined by a standardised technique in 1950-1952. The examination consisted of a single Mantoux test (10 TU RT22) and a 35-mm photofluorogram. Horwitz, Wilbeck and Erickson reported the risk of developing respiratory tuberculosis during the first 12 years of follow-up (15). Among the 286,000 natural reactors with no X-ray lesion, the annual rate of 23 per 100,000 was observed (bacillary and non-bacillary cases together).

The risk of developing bacillary pulmonary tuberculosis among those with «previous positive tuberculin; negative X-ray» was studied in Saskatchewan (Canada) during 1960-1969 (16). In 621 (67%) adults with new active pulmonary tuberculosis reported during the period under study, full information was available on the previous tuberculin and X-ray status. (The intervals between the earliest «positive» tuberculin test result and the diagnosis of bacillary pulmonary tuberculosis were as follows: more than 5 years – 71%; 4-5 years – 10%; less than 4 years – 19%.) The probable average annual risk of developing bacillary pulmonary tuberculosis in those with «previous positive tuberculin; negative X-ray» was approximately 15 per 100,000.

In The Netherlands in 1973-1975, the incidence of bacillary pulmonary tuberculosis cases among those aged 65-74 years was 14 per 100,000, and in persons aged 75 years or more it was 25 per 100,000. It may be assumed that nearly all subjects aged 65 years and over in the early 1970s must have been infected with virulent tubercle bacilli during their childhood or young adulthood because the risk of tuberculous infection was very high at the end of the last century and during the first two decades of this century. The role of exogenous re-infection in The Netherlands in the early 1970s can be disregarded, as it is estimated that only 30 persons per 100,000 were re-infected annually with tubercle bacilli at that time. Thus, the incidence rate of 14 per 100,000 among those aged 65-74, and 25 per 100,000 in subjects aged 75 years or more was to a large extent due to endogenous exacerbation.

Thus there is no doubt that in man, long after the last infection with virulent tubercle bacilli, there still exists a risk, a small one, of developing bacillary pulmonary tuberculosis. In the past, it was not possible to measure reliably the level of this risk because of a considerable and changing risk of exogenous re-infection. The role of the latter risk can be disregarded at present.

The observations mentioned above suggest that the annual risk of endogenous exacerbation causing bacillary pulmonary tuberculosis is, on average, between 15 and 25 per 100,000 natural reactors.

2) An observation showing the impact of the *high levels of tuberculosis infection rates* (and the role of *exogenous re-infection*) on the magnitude of the tuberculosis problem in the respective populations, and the close relationship between these two variables, will be mentioned.

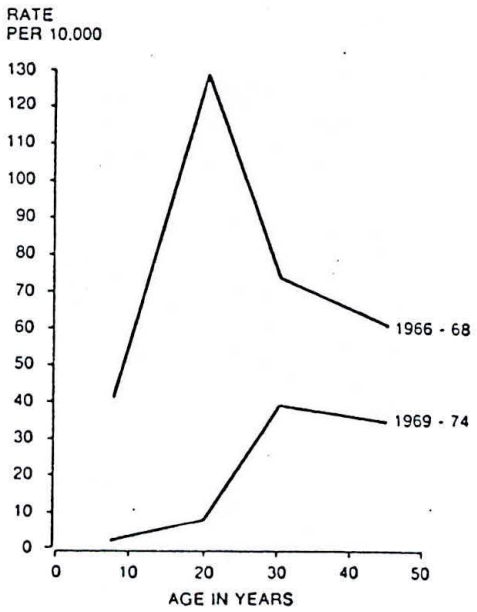
The observation concerns Eskimos in Alaska, Greenland and the North-West Territories of Canada. The annual incidence rates of tuberculosis among the native population were extremely high in all three circumpolar areas in the early 1950s, in the order of 2.0% of new (mostly bacteriologically confirmed) cases of tuberculosis each year (17). The annual tuberculosis infection rate in Alaska estimated by Comstock and Philip (18) was, at that time, as high as 25% (!), so that the vast majority of all Eskimos were infected in childhood.

The dramatic decreases in mortality and morbidity rates observed after the introduction of effective control measures in the early 1950s have been preceded, naturally, by a sharp decrease in the tuberculosis infection rates. However, the decreases in the incidence of tuberculous disease did not occur only among children and young adults but at all ages, i.e. also in persons previously infected. Thus, the same number of infected subjects aged, say, 35 years or more, in the North-West Territories of Canada produced 0.6% bacillary cases each year during 1966-1968, whereas the incidence was only 0.35% each year in 1972-1974 (17, Figure 1). In Greenland, the rates in the same age-group fell from nearly 3.0% in 1955-1957 to less than 1.0% in 1963-1965 (19). Also, in Alaska a sharp decrease in the number of new cases of tuberculosis can be observed, namely from 762 in 1952-1954 to 119 in 1970-1972 (by 84%) in those aged 25-44, and from 436 to 116 (by 73%) in those aged 45 years or more, during the same period of observation (17).

There is no doubt that the higher risk of infection in the early period must have contributed substantially, by exogenous re-infection, to the higher morbidity at that time.

Figure 1

Incidence of bacillary pulmonary tuberculosis (rate per 10,000) by age among Eskimos in the North-West Territories of Canada in two time periods: 1966-68 and 1972-74 (Grzybowski et al., 17)



RECENT ADVANCES IN TUBERCULOSIS EPIDEMIOLOGY WITH REGARD TO FORMULATION OR RE-ADJUSTMENT OF CONTROL PROGRAMMES

K. STYBLO and J. MEIJER*

Recent epidemiological studies on tuberculosis, particularly those conducted by the Tuberculosis Surveillance Research Unit, help us to understand better the way in which tuberculosis behaves and maintains itself in the community. We shall mention sudies which are related to the following items:

- the so-called «natural» trend of tuberculosis,
- the epidemiological situation of tuberculosis in the middle of this century, at present and after the turn of this century,
- impact of the present control measures on the tuberculosis situation,
- use of the basic tools for tuberculosis control at present and in future.

We cannot deal with the subjects in detail. A comprehensive report is shortly to be published in «Advances in Tuberculosis Research» (1).

1. The «natural» trend of tuberculosis

Figure 1 shows that tuberculosis mortality in Czechoslovakia, the Netherlands and Norway has

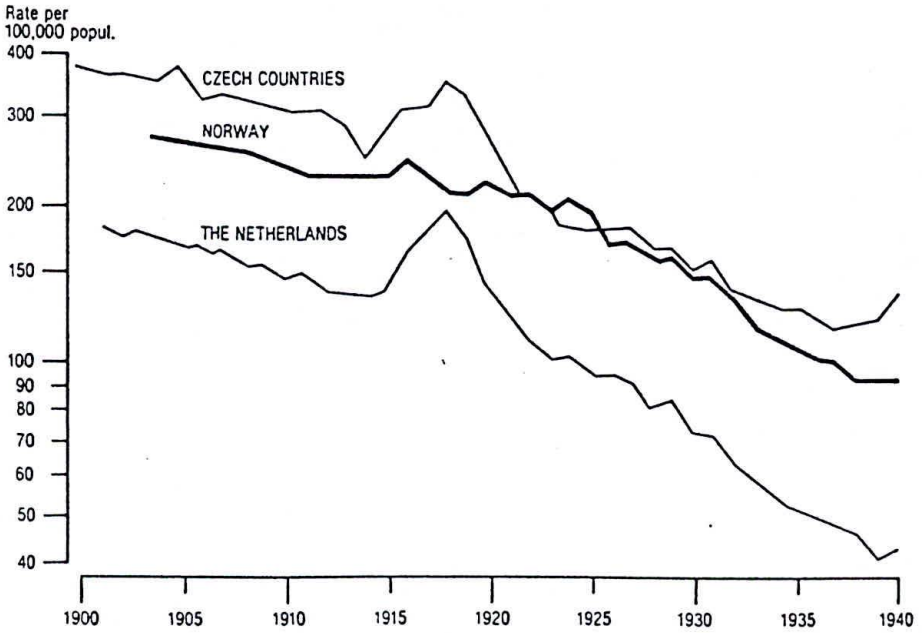


Figure 1. Tuberculosis death rates from all forms of tuberculosis in Czech countries, the Netherlands and Norway, 1900 - 1940.

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1 The annual tuberculosis infection rate indicates the proportion of the population being infected or reinfected in the course of one year.

been decreasing from at least the turn of this century. This was the case in most other *developed* countries during that period.

The observed decrease was 4-5% annually. It was *not* connected with mass BCG vaccination, chemotherapy or mass radiographic surveys as these measures did not exist at that time. Improvement of socio-economic conditions, general anti-tuberculosis measures and treatment, including isolation in sanatoria, all may have played some part in the decline of tuberculosis but one cannot assess their relative contributions. If we call this observed declining trend «natural», it is only because we have no better word to indicate that it was probably *not* brought about by specific anti-tuberculosis measures.

The same decrease is mirrored by the trend in the *annual infection rate*[1] which is shown for the Netherlands for the period 1920 to 1940 (Fig. 2).

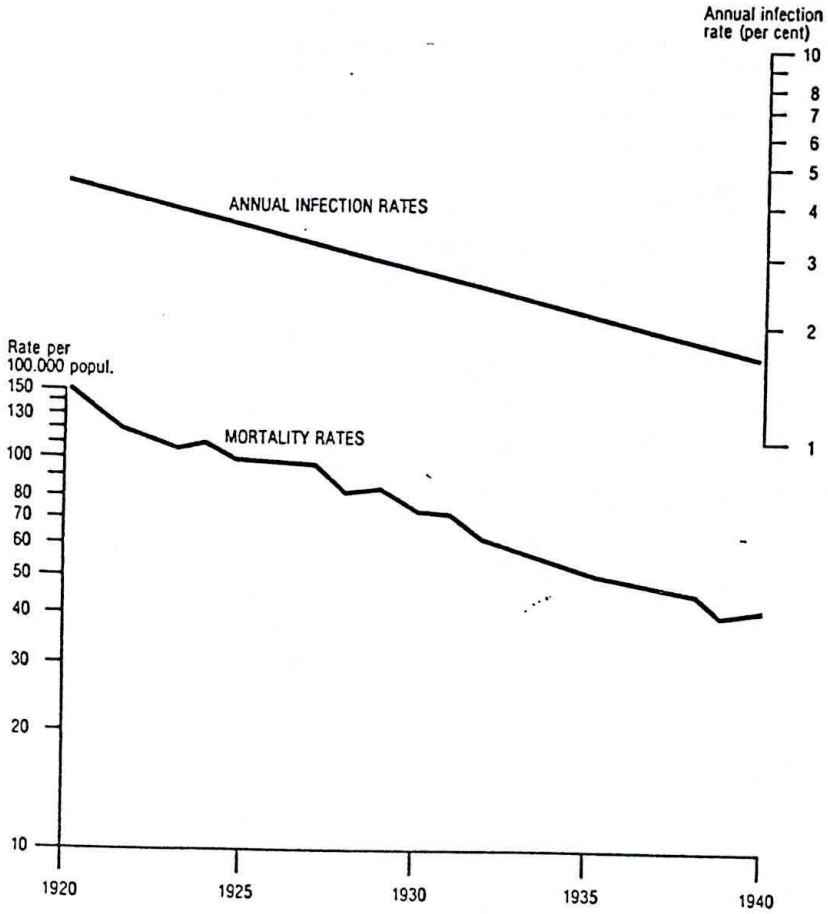

Figure 2. Annual tuberculosis infection rates and tuberculosis death rates in the Netherlands, 1920-1940.

The mortality rate fell by 5.7%, and the infection rate by 5.4% per year between 1920 and 1940.

We have introduced the annual infection rate in this context because we cannot use mortality statistics when discussing the «natural» trend of tuberculosis in developing countries.

Table 1. Estimated number of persons infected with tubercle bacilli in the Netherlands in 1910, 1920, ... 1970 and 1975.

Year	No. of infected/year (per 100,000 population)
1910	11,310
1920	6,690
1930	3,920
1940	2,080
1950	530
1960	133
1970	45
1975	25

The third curve shows similar figures to be expected in the year 2005. Only 25% of those aged 70 years will have been previously infected and about 50% of those aged 80 years.

The percentage of infected subjects for the years 1945, 1975 and 2005 given per age group in Figure 5 can also be expressed in terms of the general population. The upper part of Figure 6 shows the composition of the general population in the Netherlands in 1975, by age. The lower part of

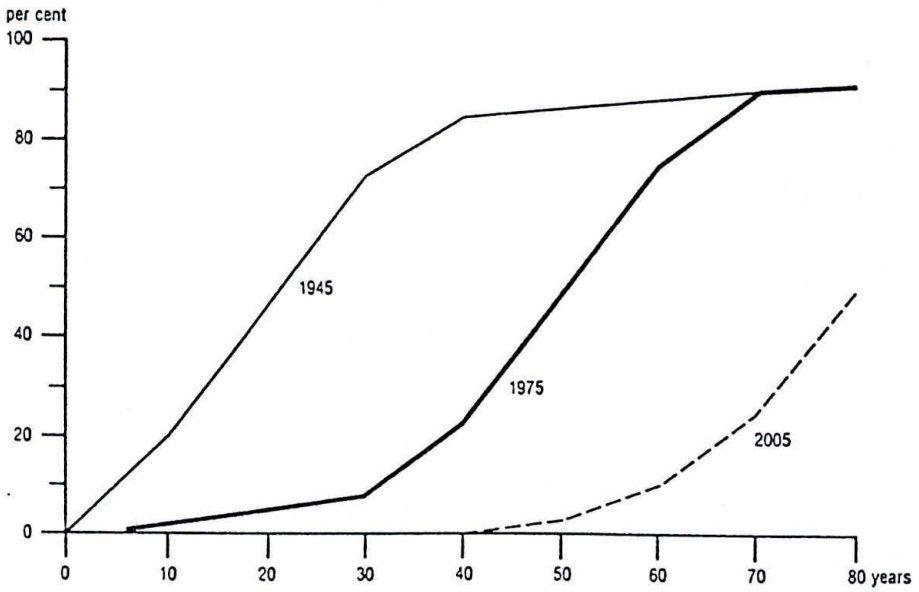

Figure 5. Estimated prevalence (per ct.) of tuberculous infection, by age-groups in 1945, 1975 and 2005, the Netherlands.

Figure 6 shows that between 1945 and 1975, the proportion of the total population infected with tubercle bacilli fell from 59% to 26%. In the year 2005, the proportion of infected is expected to be 5%.

In our opinion, similar trends may be expected in other developed countries.

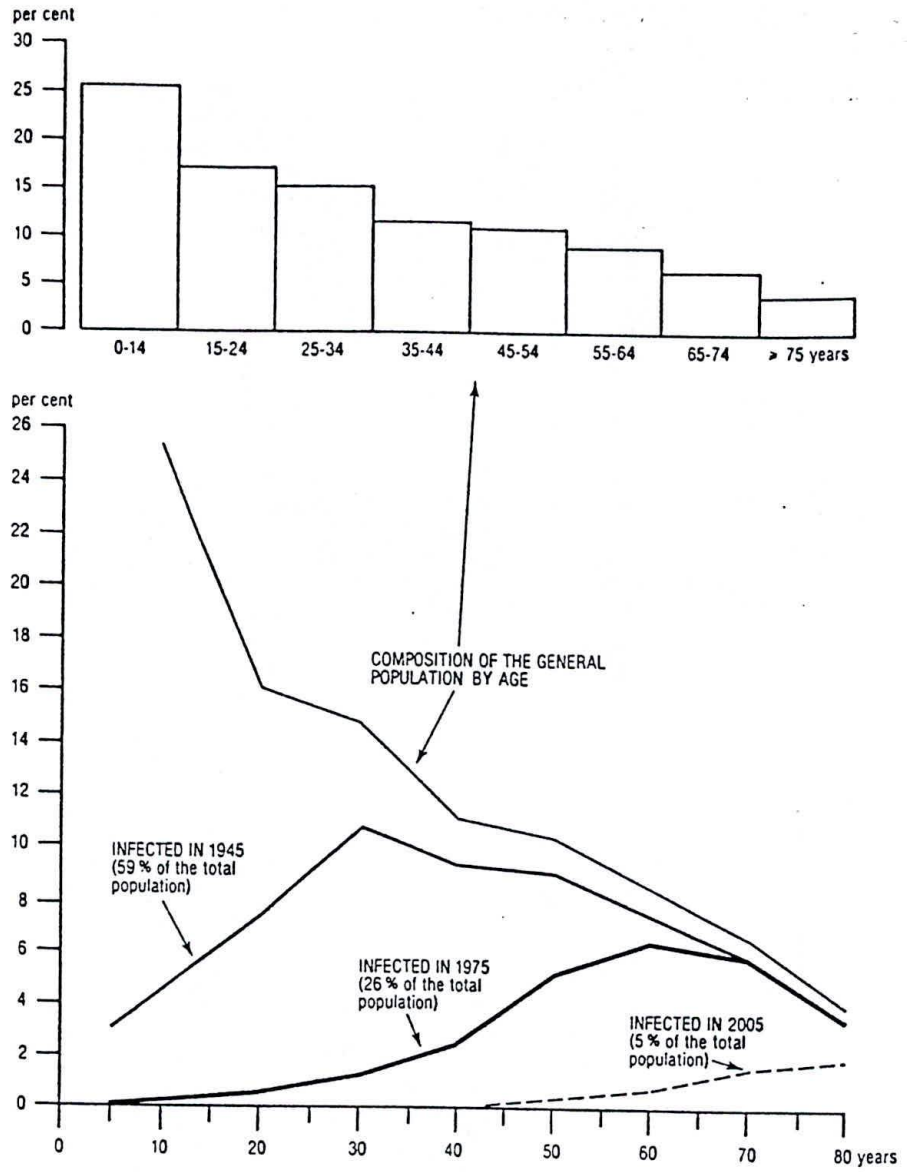

Figure 6. Distribution of the general population in 1975 and estimated prevalence of tuberculous infection per 100,000 population in 1945, 1975 and 2005, the Netherlands.

There is evidence that in some *developing* countries a moderate decrease has occurred in the tuberculosis infection rate but, in others, the risk remains nearly constant or decreases very slowly. If the annual infection rate remains constant, the proportions of the population infected at a particular age remain the same for each cohort.

Figure 7 (the left-hand curve) shows the prevalence of tuberculous infection, by age-groups, if a constant infection rate of 3% is presumed. At age 10, about one-quarter of children will already

Developing countries usually have no reliable information on tuberculosis mortality. The main material for studying the natural history of tuberculosis in these countries comes from the results of WHO tuberculosis surveys in the 1950's and 1960's. The material collected by the WHO teams is of high quality.

In a few of the countries, tuberculin testing was repeated several years after the WHO survey, so the trend of the tuberculosis situation during the interval can be estimated. Figure 3 shows that often there was little, if any, downward trend in the annual infection rates; in these countries, there are virtually no «natural» decline. But we know that *if* in such countries specific control measures are taken up, a decrease *will* be observed (Morocco, urban districts: see Figure 2 of M. A. Bleiker and K. Styblo's article, *ibidem*, pages 295-298).

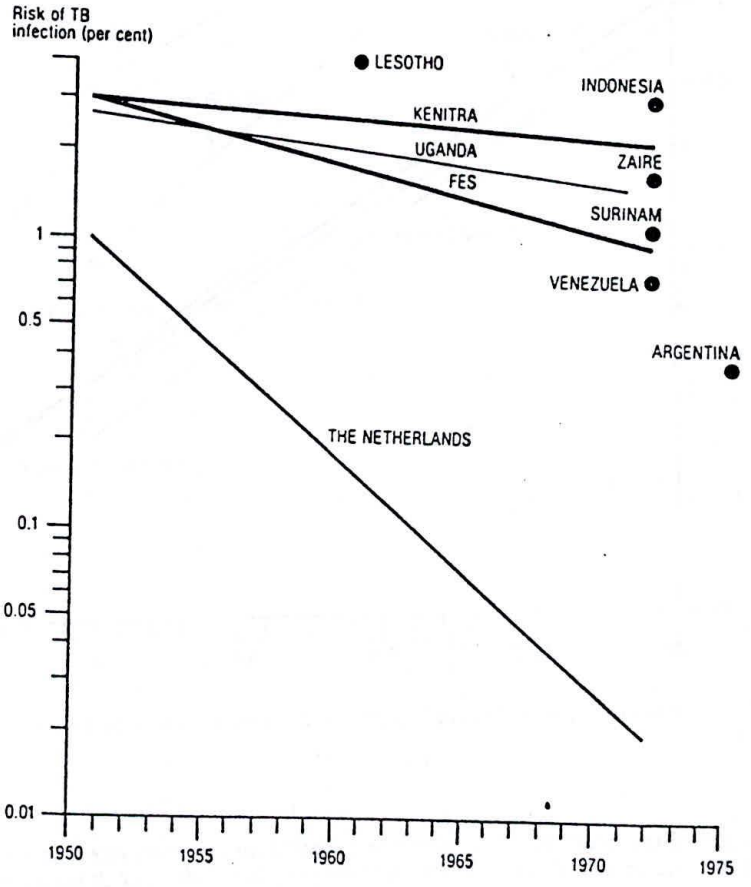

Figure 3. Estimated annual risk of tuberculous infection, 1950 - 1971 or 1975.

2. *The epidemiological situation of tuberculosis in the middle of this century, at present and after the turn of this century*

We shall focus on the size of the tuberculosis problem and on its trend. We shall do this *not* by presenting data, such as incidence figures from different countries, as these data are not always reliable, but shall instead use the annual tuberculosis infection rate as the index of the size of the tuberculosis problem and its trend.

We now have information on the annual infection rates and their trends in 6 countries or areas, as shown in Figure 4. Two main conclusions are drawn:

have no data on the impact of control measures on the tuberculosis situation for developing countries. So we will only discuss *developed* countries.

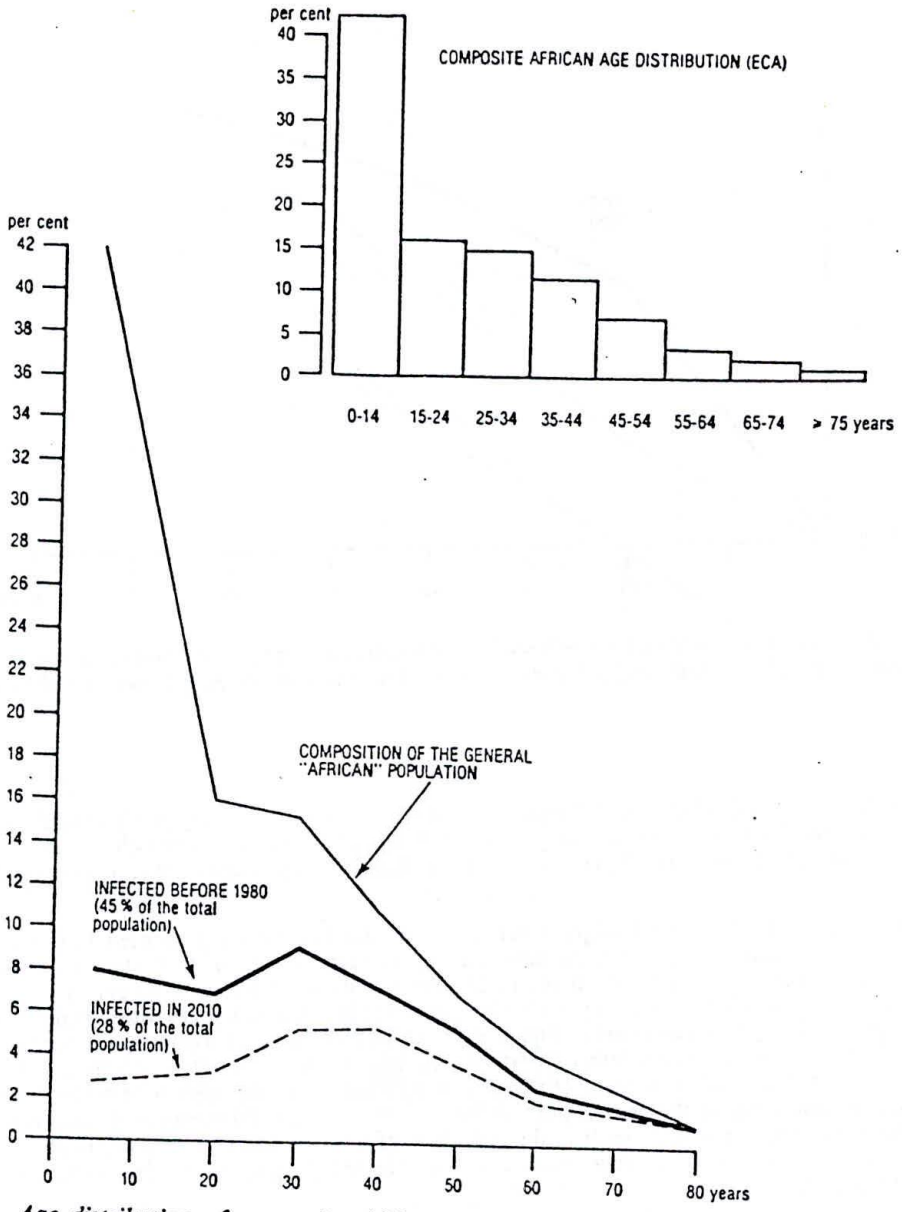

Figure 8. Age distribution of composite African population (ECA) and estimated prevalence of tuberculous infection per 100,000 population, before 1980 and in 2010.

When trying to assess the impact of specific control measures in developed countries, one has to keep in mind the «natural» decline, which has already been mentioned. The effects of control measures are - so to speak - superimposed on the «natural» trend.

The two basic tools used for tuberculosis control are BCG vaccination and case-finding/treatment.

3.1. BCG vaccination

There is general agreement that BCG vaccination has a high «direct» effect by preventing the development of tuberculosis. This «direct» effect may be measured in terms of the proportion of cases prevented in the vaccinated age-groups.

It is also claimed that mass BCG vaccination - especially at school-leaving age - will influence the chain of transmission and so prevent the development of tuberculosis in *unvaccinated* subjects. This is what one may call the «indirect» effect of BCG vaccination.

We have studied the indirect effects of BCG, given at ages 15-29 years, on tuberculosis among the unvaccinated children of vaccinated parents. The trend in the incidence rates of tuberculosis (all forms) among children aged 0-4 and 5-14 in the Netherlands where mass BCG vaccination was never applied was of the same order as that in Norway where it had been given to school-leavers since the early 1950's (Fig. 9; shown for children aged 0-4 years only). We have also made a theoretical assessment of the indirect effects of a mass BCG vaccination programme. This showed that the effect of BCG in preventing *infectious* cases is between 0.3 and 2.0% annually only. For details, reference is made to the paper published in *Tubercle* 1976 (2).

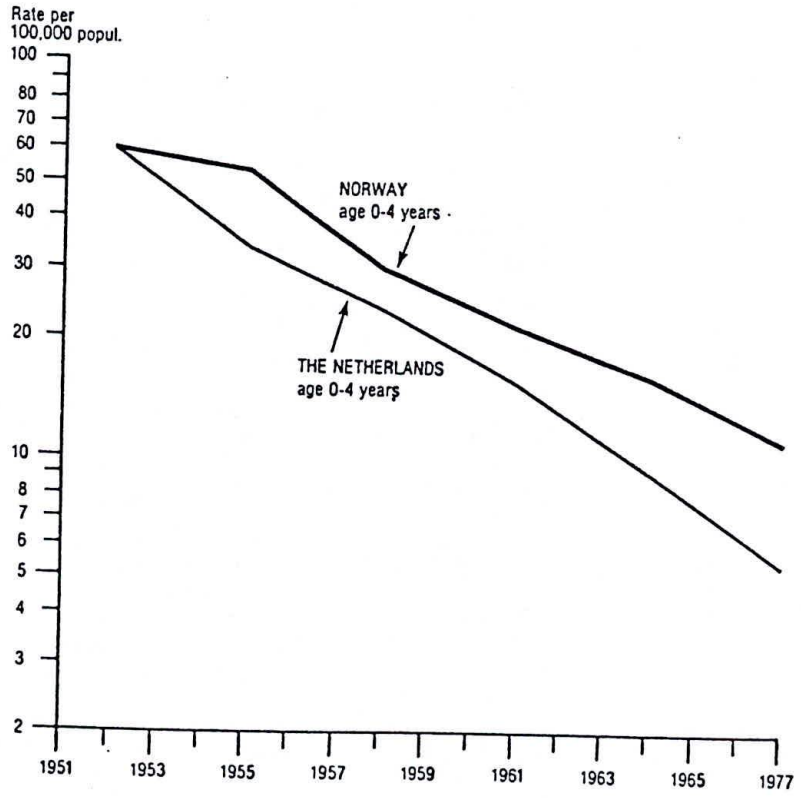

Figure 9. Notification of tuberculosis (all forms) in children aged 0 - 4 years. Norway and the Netherlands, 1951 - 1968.

The main error in the postulate that BCG vaccination would have a considerable impact on the transmission of infection is due to the *incorrect assumption that a case of tuberculosis prevented by BCG vaccination is identical with a prevented source of infection.* However, more than 95% of tuberculosis cases in children, and 75% of cases in subjects aged 15-29 years which should have been prevented by BCG vaccination, are smear-*negative.* As the high protection induced by BCG vaccination is limited in time, the vast majority of newly developed smear-positive cases of pulmonary tuberculosis among the general population cannot be prevented by mass BCG vaccination.

3.2. Case-finding/Treatment

The most powerful weapon in tuberculosis control is case-finding and chemotherapy. It is considered as an entity, as case-finding is a preliminary to treatment and cure.

It is easy to measure the effect of chemotherapy in a group of bacillary patients. But what is its effect on the overall tuberculosis situation? In other words: to what extent do case-finding and chemotherapy influence the infection rate? This is more difficult to answer as the trend in the tuberculosis infection rate mirrors several factors: (1) the «natural» trend; (2) some effect of BCG vaccination; and (3) the effects of case-finding and chemotherapy. Even if we observe those developed countries where no mass BCG vaccination was done, we shall not be able to estimate the «pure» effect of case-finding/treatment but can only make an intelligent guess.

Our best estimate is that case-finding and treatment in developed countries during the last two or three decades may have accelerated the decrease of the problem by 7-8% annually. This percentage superimposed on the 4-5% annual «natural» decrease results in a total decrease in the tuberculosis infection rate of about 11-13% each year, as shown previously (Fig. 4). Such a decrease was observed both in developed countries with and those without a mass BCG programme.

4. Use of the basic tools for tuberculosis control at present and in the future (here we return to the separate presentation for developed and developing countries)

The two basic tools used for tuberculosis control are BCG vaccination and case-finding/treatment.

In *developed* countries *mass BCG vaccination* will be discontinued when its complcations outweigh its benefits. In the Netherlands with *no* BCG vaccination, the present annual rate of the disease is about 4 per 100,000 in children aged 0-14 years. In this situation, mass BCG might do more harm than good.

Chemoprophylaxis is not discussed in our contribution, as we think that it will have a very limited use in future. It will continue to be given to converters in high risk groups, such as contacts of smear-positive sources.

We shall not go into the subject of *chemotherapy.* There is evidence that at least in some developed countries, the results of chemotherapy observed under routine conditions are nearly as good as those obtained in controlled clinical trials (3,4). However, we would point out the danger of the disappearing know-how on chemotherapy among the medical profession.

Diagnosis of the continuously decreasing number of new cases of tuberculosis will remain the *most difficult problem.* Physicians will «forget» tuberculosis in their daily practice because they will seldom see it. In some developed countries, three-quarters of the general population are at present uninfected and thus tuberculin-negative. Such countries should introduce wide usage of the Mantoux test into the daily work of some hospital departments and other health services.

It seems unavoidable that some persons with symptoms caused by tuberculosis will seek medical advice too late or not seek it at all. Also, in a proportion of cases, the doctor's delay in diagnosing tuberculosis may be considerable.

It goes without saying that mass indiscriminate radiography will have no place in any future tuberculosis programme.

In *developing* countries, case-finding and treatment of smear-positive cases of tuberculosis at all ages and direct mass BCG vaccination of children should both be applied as widely as possible. These two tools must be used for several decades.

Experience shows that *mass BCG vaccination* at birth is not feasible in most developing countries. At present, single direct BCG vaccination at school-entrance age will probably be the policy of choice.

At present, the situation regarding *case-finding* of persons with smear-positive pulmonary tuberculosis is very unsatisfactory, and intensive operational research in this field is urgently needed. However, even an improvement in identification of smear-positive cases, for instance from 30 to 50%, will considerably increase the impact of the control measures on the overall tuberculosis situation.

As to chemotherapy programmes, Table 2 shows that in some developing countries quiescence of the disease was achieved in only 60-65% of all patients (5). The fatality rate was about 10-16%, and the proportion of chronic bacillary excretors remained high (about 25%). In many developing countries, the success rates may be even worse. Fox estimates that they can fall to levels of the order of 50%, if the relapsed cases are taken into account (6).

Evidently, *long-term* chemotherapy of tuberculosis is beyond the resources of nearly all developing countries. We would plead for reduction of the cost of rifampicin so that *short-course* chemotherapy might be widely applied in most developing countries.

Table 2. Fate of bacillary cases of tuberculosis when treated under mass chemotherapy programmes in certain developing countries.

Country	No. of cases	Year	Duration of follow-up	Percent died	Bacteriology	
					% Pos.	% Neg.
Taiwan	237	1968	2 years	10.5	24.1	65.4
Korea	288	1968	1.5 - 2 years	11.1	26.0	62.9
Kenya	739	1968	> 1 year	15.6	21.5	62.9
India	292	1974	1 year	9.6	27.0	63.4

Source of information: Grzybowski, S. et al.

We had only 25 minutes to deal with a very large subject and therefore this presentation has to be considered as an abstract. For those who are interested in this subject, we would refer to the forthcoming report in «Advances in Tuberculosis Research» (1).

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Epidemiological Research in Tuberculosis Control

Introduction

Growing concern is being expressed about the fact that the tuberculosis control programs introduced in developing countries, now some 20 years ago, apparently fail to produce a noteworthy reduction of the problem *(1)*. Although it is generally recognized that these programs still have many shortcomings, there is a conviction that they will reduce transmission and thus cause a gradual decline.

The implied assumption that the trend of the tuberculosis problem is a suitable indicator of the achievements of a tuberculosis program perhaps should not be accepted uncritically. In Europe and North America a decline in tuberculosis set in long before the introduction of any specific antituberculosis measures. A pronounced change in the declining trend of the risk of infection was observed in the mid-1940s in many developed countries, with the discovery and widespread use of streptomycin for the treatment of tuberculosis. Whereas this no doubt caused a reduction in case-fatality, it should be noted that the ensuing reduction in the risk of infection also coincided with the upsurge in socioeconomic development after World War II. Then the rate of decline jumped suddenly from 3-5% to 10-14% a year, and this rate has been almost constant until now *(2)*. Some discrepancies in this pattern have been observed. In the Netherlands, the sudden change took place a few years before the discovery of chemotherapy; one explanation advanced is that the decrease was caused by the compulsory pasteurization of milk enforced by law in 1940 *(3)*. In Finland two abrupt changes were observed, one from 3.5% to 8.5% in the mid-1940s, and a second, doubling the rate of decline, to 16% in 1966 *(4)*. No plausible explanation has yet been found for this observation.

Before chemotherapy, certain measures were applied which probably had some effect in limiting the spread of infection, such as the early diagnosis by radiography and the isolation of patients in hospitals. Artificial pneumothorax might have had bacteriological benefits too. It is impossible to separate by retrospective analysis the epidemiological impact of these measures from that of the continuous improvements in the standard of living for the period. No estimates of the risk of infection are available before 1910, but the steadily declining mortality curve does not show any change attributable to the introduction of a specific intervention. For instance, in England there was a gradual increase in the annual rate of decline in mortality from tuberculosis during the period 1851-1946 of almost 1% to 2% but no modification in this trend was seen when the tuberculosis services were established and developed *(5)*.

In some developing countries, especially in Latin America, in the Western Pacific ridge, and the oil-producing Arab states, a modest annual decrease, in the rate of 2-5%, of the tuberculosis problem is probably occurring. These are countries with an intermediate level of socioeconomic development. Thus the attribution of all the credit for the decline to the tuberculosis programs, either in developed or in developing countries, is largely unwarranted.

A distinction must be made between epidemiological surveillance and program evaluation. Whereas

creased by about 25% in spite of the fact that case-finding improved consistently during the period *(16)*. The project provided extensive case-finding facilities, but no other treatment was made available than the standard regimens of one year's duration recommended by the national tuberculosis program.

Several of the more affluent developing countries have witnessed a decline in the tuberculosis problem, but invariably the coverage and quality of the health system has been quite high and extensive use has been made of X-ray and cultures for the diagnosis of tuberculosis, at least in the urban areas. And even then, the question of how much the decline is actually produced by the program and how much occurs as a result of general socioeconomic development is difficult to answer.

All developing countries, for social reasons, must give priority to affording immediate relief from suffering. Still, in formulating programs to attain the latter objective they would wish to select techniques and strategies that are also propitious to achieving a gradual reduction of the program and thus a durable social benefit. Any reduction in the risk of infection would have a relatively rapid effect on the incidence of childhood tuberculosis, a problem given little attention so far, which is not directly alleviated by the basic case-finding and treatment programs. Current programs notably appear not to eliminate intrafamiliar transmission of infection. Quantitative information on the magnitude of the problem in children, and on the epidemiological significance of infection in childhood, is badly needed.

The Impact of Various Control Measures

BCG Vaccination

It seems scarcely worth discussing this subject at a moment when serious doubts have been raised about the efficacy of BCG, but its potential epidemiological impact retains its interest. Extrapolating from findings in Europe, in particular from a large trial in England, it seemed that BCG vaccination not only could reduce considerably the incidence of tuberculosis in adolescents and young adults but also prevent an appreciable proportion of new sources of infection. Observations in other areas, however, did not substantiate this point of view. In the BCG trials in the United States, and very much so in the trial in India, new infectious cases of tuberculosis almost entirely occurred in the already infected population; during the first two and one-half years of the follow-up of the trial in India only some 4% of the cases of infectious tuberculosis had been potentially preventable. Thus, even mass vaccination with an effective vaccine could not possibly produce a significant immediate impact. A sustained vaccination program could produce an impact in the long run if the protection from BCG were appreciable and long lasting. This matter still needs to be studied, but it should be clear already that especially vaccination of the newborn will not prevent many sources of infection in situations where infectious tuberculosis is mainly a disease of late adulthood. The current priority is to investigate the protective effect of BCG vaccination against childhood tuberculosis in tropical and subtropical areas. Especially since young children do not benefit directly from efforts to detect and treat infectious pulmonary tuberculosis, BCG vaccination retains its potentially important role in the control of tuberculosis in children. A comprehensive program has been started by WHO to evaluate the effectiveness of BCG vaccination programs in young children and to identify and quantity factors and determinants that may influence the efficacy of BCG, including the characteristics of various strains of *Mycobacterium tuberculosis,* the role of exogenous reinfection, the host response, and environmental mycobacteria.

Passive Case-finding by Microscopy, Followed by Treatment

Currently this is the main control measure applied in developing countries. Microscopy fairly reliably gives a positive result if there are large amounts of bacilli in the sputum. Therefore it is considered that microscopy can discover, and subsequent chemotherapy will remove, the most important sources of infection. This in turn should reduce the risk of infection and thus the number of new cases arising among the noninfected. The question is—how much?

The matter appears to be an intricate one. In developed countries, with extensive case-finding activities and almost maximum treatment results, there has been a decline in the risk of infection in the order of 12-14% per year, of which some 7-9% have been attributed to the control program. The part played in this rather modest reduction[2] in the transmission of infection by the diagnosis of self-

[2]The reduction is considered very modest when compared with the effectiveness of other public health programs such as smallpox and measles immunization and chlorination of municipal water supplies, by which the transmission of infection is reduced by almost 100% in one year.

reporting smear-positive patients and their treatment is unknown. In developed countries many persons were treated on radiological evidence or when their sputum was positive on culture only. A significant proportion of these cases would have become smear-positive if left untreated, within a relatively short period of time. The removal of these potential sources of infection may have had a far larger epidemiological impact than that of the self-reporting established sources.

In the European countries disease used to occur relatively shortly after infection, so that a reduction in the risk of infection was soon to be followed by a reduction in incidence. Thus, the removal of sources of infection had a noticeable indirect effect. However, if a small reduction in the risk of infection is obtained in a situation where both the prevalence of infection is high and the interval between infection and disease is long, there may not be any measurable impact on the incidence for several decades.

Thus the effect on the epidemiological situation of passive case-finding by microscopy and treatment may be very small. It therefore appears of great interest to conduct prospective studies of the relative epidemiological merits of diagnosing and treating different categories of pulmonary tuberculosis, and to study the effect of introducing different case-finding strategies and diagnostic techniques.

Once an infectious case of tuberculosis has been detected it remains to be treated effectively if a source of infection is to be removed. In developing countries treatment often remains deficient, and this obviously further reduces the epidemiological impact of the program. In actual fact, the impact may be less than suggested by the proportion of patients cured; defective treatment may prolong the infectiousness together with the life of the patient. It would appear difficult to study this matter in isolation, but one attempt in Madanapalle, India, tended to show that an extended inefficient treatment program in fact produces an increase, both in the prevalence of tuberculosis and the risk of infection *(17)*, which seemed, in epidemiological terms, worse than not to treat at all. Surveillance of tuberculosis infection among contacts of patients may provide information on this matter.

Awareness and Motivation

An inherent weakness of the passive "case-finding" method is that it relies entirely on patients having to be aware of the fact that they are ill and being sufficiently motivated to seek relief at the right address. In these respects the situation in developing countries is on the whole much less favorable than it used to be in technically advanced countries. Only a fraction of the patients come to the attention of the competent health services. Moreover those who are positive only on culture remain undiagnosed until they possibly become smear-positive. Follow-up is therefore essential.

Increasing the awareness and motivation through health education, but also by providing adequate relief for respiratory complaints other than tuberculosis, may bring about significant improvements in the effectiveness of case-finding, especially if the quality of microscopy is high and can be complemented with culture examination. The development of primary health care, and in particular of active community participation, offers new prospects for achieving adequate levels of awareness and motivation. The returns of efforts in this field may be studied in comparison with those of further improvements in the specific control measures.

Smear and Culture Examination

Any diagnostic test discovers severe cases of disease more readily than mild cases. For this reason microscopy appears an acceptable technique in programs relying on passive case-finding, and probably also if a hard screening test is applied. Still, when the prevalence of tuberculosis among symptomatics is low, the method not only becomes impractical, but would also produce false results, as was demonstrated in Papua New Guinea, where among highlanders 1,400 smears would have to be examined to find one positive result, and the chance of this one being tuberculosis would be as little as 1.1% *(18)*. With increased awareness and motivation the effectiveness of microscopy as a diagnostic test will diminish as the prevalence of disease among those examined reduces, and the yield of case-finding actually may not noticeably increase unless a more sensitive diagnostic measure is introduced. It has been demonstrated that if health education shortens "patient's delay" in diagnosis, "doctor's delay" increases to the extent that the overall effect is negligible *(19)*. Studies on the sensitivity and specificity of smear microscopy as compared with culture examination need to be carried out under different program situations, preferably in connection with studies on the epidemiological significance of the various categories of patients.

X-ray Examination

In developed countries X-ray examination has been used for two distinct purposes: diagnosis and mass screening. Although not strictly pathognomonic, X-ray examination proved a suitable test in serious cases of disease, but in mild and early cases both sensitivity and specificity are much reduced. The latter results in a low effectiveness in populations where the prevalence is low, as was confirmed in mass screening in developed countries.

Diagnostic use of X-ray examination was not recommended as a priority for developing countries, since in passive case-finding approximately similar results can be obtained with sputum microscopy, which is much cheaper. Also mass X-ray screening was considered incompatible with a situation in which the first felt need of the population, i.e., diagnosis for persons with symptoms, and adequate treatment for patients, is not yet satisfied.

As a diagnostic facility at the referral level of the general health service, X-ray examination makes it possible to examine patients whose sputum is negative on smear examination, and thus to obtain further information in cases with unexplained chest symptoms. If adequate treatment facilities have been established at the community level, X-ray examination of high-risk groups would make it possible to discover at least a large proportion of the prevalence cases. Obviously the relative inefficiency of mass X-ray observed in developed countries should not be extrapolated to developing countries, but the matter should be examined under local circumstances.

Conclusion

Reviewing the epidemiological basis for tuberculosis control in the light of more recent observations, a number of approximations and plain gaps in knowledge appear to call for prospective quantitative epidemiological research into several issues. In particular the concept that control measures aimed at attaining the primary social target of control will also bring about a reduction of the problem, seems worth investigating. The relative importance of alternative measures will become relevant when developing countries will have the opportunity of extending control beyond the first priority stage, which is likely to occur with the widespread effective coverage of primary health care. Practical methods for program evaluation and surveillance need to be described if the situation in developing countries is to be duly appreciated in the future.

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(Source: H. G. ten Dam, Scientist, and A. Pío, Chief, Tuberculosis and Respiratory Infections Unit, WHO, Geneva.)

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Epidemiological Assessment of Tuberculosis. Trends in Some Countries of the Americas

Introduction

The continuity of the tuberculosis transmission chain that keeps the disease endemic in the population depends on multiple factors. Prominent among them are the prevalence of sources of infection, mainly, cases of bacillary pulmonary tuberculosis; the number of persons infected by each case; and the probability of infected individuals contracting the disease as a result of infection.

The number of infected persons per case depends on the site and type of tuberculosis and the behavior of the patient. The number of exposed persons and the degree of exposure, which in turn depend on population density and type of housing, also influence the number of infected persons. The probability of contracting the disease depends mainly on the infecting dose and on the immune status of the host, and therefore, on age, sex, nutrition and concomitant diseases. In relation to the latter it is well known, for example, that diabetes and the use of corticosteroids increase the risk of acquiring the disease. Similarly, infection with human immunodeficiency virus (HIV) significantly increases the risk of contracting tuberculosis (usually about 10%), among infected persons. Infection with HIV interferes with the cellular immune mechanism responsible for destroying mycobacteria. In developed countries such as the United States of America, the age group infected with tuberculosis and infected with HIV do not overlap much; in developing countries, however, both infections have greater prevalence in young adults, which could bring about an increase in tuberculosis if HIV infection spreads. In Brazil, 17% of the AIDS cases are discovered through tuberculosis.

In developed countries, improvement of socioeconomic conditions contributed to a gradual reduction of approximately 5% annually of endemic disease; and when control measures such as diagnosis, treatment, vaccination and chemoprophylaxis were added, this reduction reached 14% annually in countries with better health programs(*1*). The decrease in mortality from tuberculosis in the countries of nothern Europe and the United States of America began at the end of last century, long before chemotherapy. In less developed countries, however, the effect of socioeconomic development is much smaller and a decrease in endemic disease does not occur without an effective control program. This control program must have enough coverage and quality to be able to break the transmission chain. Although the latter goal is more difficult to attain, the impact of such a program may be greater in a developing country. In developed countries the disease occurs among the aged population, as a consequence of old infections, and cannot be prevented by the principal control activities.

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Epidemiological Indicators

In general, evaluation of the status of tuberculosis is based on a combination of estimates of three indicators, i.e., risk of infection, incidence, and mortality, along with knowledge of socioeconomic and sanitary conditions in the country and the quality and coverage of program activities. The most frequently used indicators are discussed below.

Risk of infection, or the probability of an individual being infected in a year. Obtaining this indicator requires prevalence studies of infection, with tuberculin tests in representative samples of the child population, repeated at several years intervals. This is the most useful indicator; however, vaccination with BCG, infections with nontuberculous mycobacteria and the mobility of the population make its obtention difficult.

Case incidence, especially of smear positive pulmonary tuberculosis in young adults. This indicator is useful only when the case detection program achieves good coverage, its intensity is maintained relatively constant, and there is good reporting and quality of registration .

Mortality. This indicator is greatly affected by the program for case finding and treatment, and usually decreases more rapidly than transmission. In the absence of control measures its trend is similar to that of the risk of infection and incidence. It is useful as an indicator in countries with high mortality where mortality reduction is a priority objective.

Current Situation and Trends in Incidence and Mortality

In 1983 an analysis of the information available on annual reported incidence of new cases and mortality from tuberculosis in countries of the Americas with more than 100,000 population was performed at the PAHO/WHO Regional Office. The work was done with the cooperation of the WHO Collaborating Center for Tuberculosis Epidemiology in Santa Fe, Argentina. The resulting document was distributed to countries with the request that they provide the Collaborating Center, on a regular basis, with annually updated information on reported cases by age, site and bacteriology; and on mortality by age. With those data a second document(*2*) was prepared, on which this paper is based.

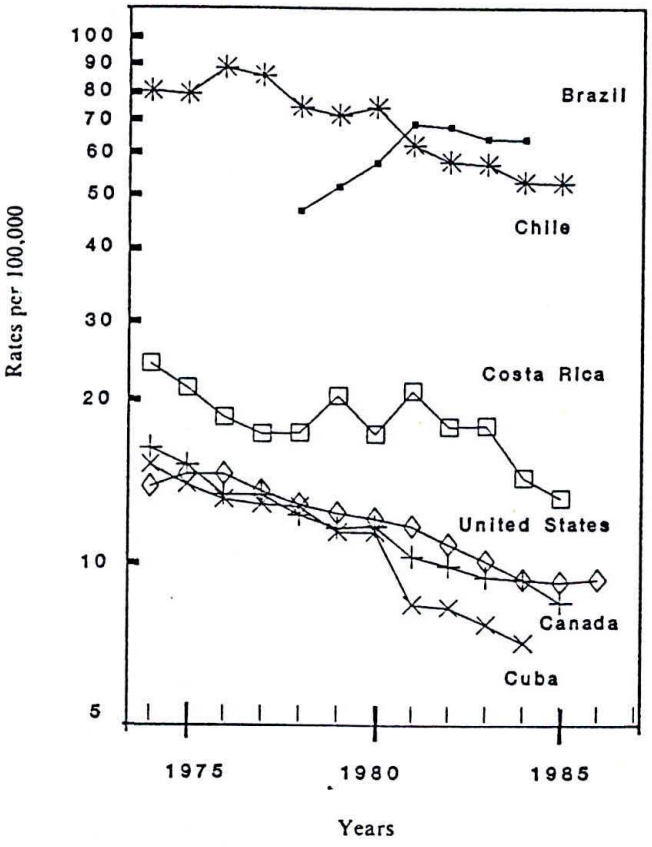
In general, for the population of the developed countries in the Region—Canada and the United States of America—annual reductions of nearly 6% in the risk of becoming ill from tuberculosis are estimated. These countries lack an "active" control program with national coverage, but have ample resources for highly effective diagnosis and treatment in addition to the historical trend resulting from their socioeconomic development. In recent years reported incidence in the United States has stabilized at 10% above expected figures. The two most important factors affecting this trend are the immigration of persons with a greater prevalence of infection and risk of becoming ill—from countries of Southeast Asia and Latin America—and the rapid spread of infection with HIV.

In countries of Latin America the trend varies according to the level of development, quality of the health care system, and coverage and quality of control measures. The average reduction is estimated at 6% annually. There is a latent period of several years between improvement or deterioration of program activities and its reflection in the indicators. Hence a program with improved organization will initially produce an increase in reported cases—especially smear positive—followed by a reduction in mortality and a stabilization of reporting, then a reduction in incidence, greater among young people. It should be reiterated that the epidemiological indicators cannot be interpreted independently of operational factors of the programs, especially with respect to data obtained from the notification registries.

Trend differences in Latin America can be illustrated by the tuberculosis situation in some countries (Figure 1). Cuba, for example, has a good health care delivery system and a well-organized tuberculosis control program; coverage of practically 100% of children with BCG; case finding among patients with respiratory symptoms who consult the general health services, through sputum smear and culture; and treatment with high compliance. The result has been an annual reduction of incidence of 9.6% since 1978, and juvenile tuberculous meningitis has not been observed for 10 years. The incidence level reached is similar to that in Canada and the United States, although the average age of cases is lower.

On the other hand, Costa Rica, with a much slower reduction—approximately 6% annually in incidence before 1975 and around 9% annually in mortality—has also reached very low levels. This is partly explained by an effective, ongoing program, although of limited coverage in some areas due to lack of integration of symptomatic case finding into the social security health services system. From 1977 to 1983 sharp increases in reporting and a continued decline in mortality were observed; this can be interpreted as an increase in diagnoses—in large measure through immigration due to political instability in Central America—followed by good treatment of the cases detected. A reactivation of the

Figure 1. Reported incidence of tuberculosis (per 100,000 population) in Brazil, Canada, Chile, Costa Rica, Cuba and the United States of America, 1974-1986.

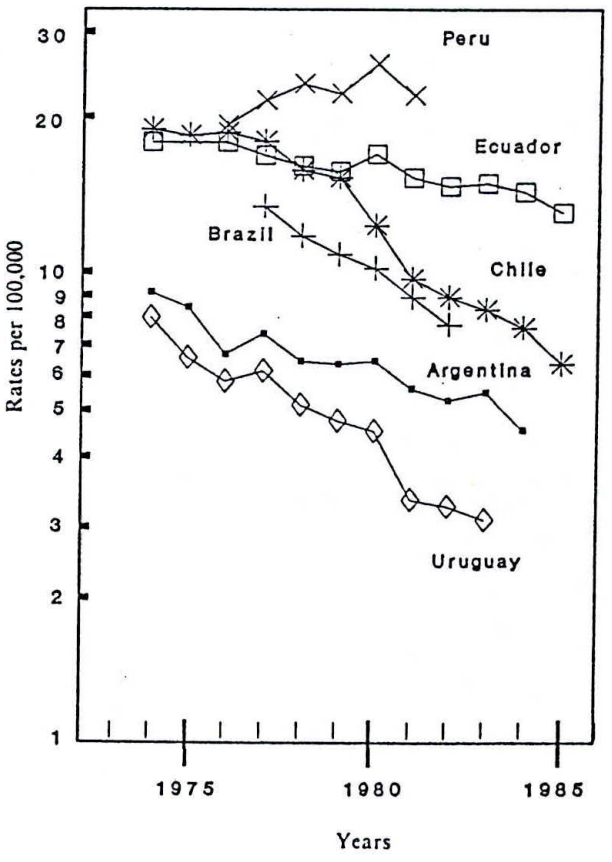


program, currently in progress, should give rise to a new peak in the detection of cases.

In Brazil the existent program, which had less than 600 health services units and approximately 23,000 specialized beds, was gradually merged into the general health services of the States in the 1970s. Currently approximately 4,000 health services units are incorporated into an integrated program, with less than 3,000 specialized beds, almost all in general or chest hospitals. At the same time, notification increased from 47,000 cases in 1974 to 88,000 in 1984 and stabilized at an estimated 80% of the real incidence that can be detected with the technology available in the country. Information at the national level represents an average of the trends and levels of the problem, as well as of the coverage and quality of information, in the individual States. An average minimum reduction in real incidence of 6% annually can be assumed; mortality in state capitals, on the other hand, is declining by 11% annually, which is probably a good reflection of the national trend (Figure 2). The annual risk of infection is estimated at approximately 0.9%, ranging from 0.2% in the south to 2% in the north of the country.

In Chile the intensity of case finding efforts has increased yearly. This may be observed through the annual number of sputum smears performed in the country for diagnosis of tuberculosis. Treatment has also improved, currently utilizing an abbreviated scheme of seven months including just one month of daily treatment with completely supervised administration. As a result of the real reduction in incidence and greater case-finding efforts, the reported incidence decreased gradually by 5.6% annually from 1976 to 1985, while the yield, as measured by the proportion of positive sputum smears, decreased rapidly. Mortality decreased by 9.9% annually between 1981 and 1985.

Figure 2. Tuberculosis mortality (per 100,000 population) in Argentina, Brazil, Chile, Ecuador, Peru and Uruguay, 1974-1985.



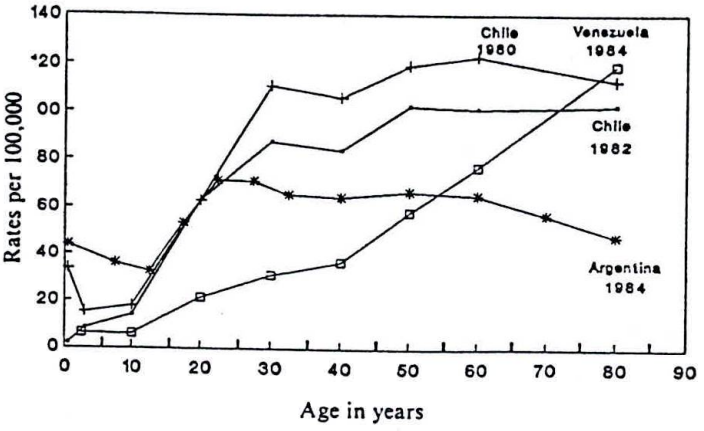
It is more difficult to interpret data from countries where the program and the information systems are inefficient. In Mexico, for example, it is estimated that less than half the cases are reported; 10 years ago the number of reported cases was almost the same as the number of deaths registered by the vital statistics system. The increase in reported cases is not due to extension of the program but to the incorporation of the cases treated by the Social Security health care system into the reports of the services of the Ministry of Health. The 7% annual reduction in reported cases from 1974 to 1978, when there were no changes in the program, may be real; however, this would not be true for real incidence rates which are probably much higher.

In countries with high incidence such as Haiti, Bolivia, Paraguay and Peru, the problems of coverage of the health infrastructure coincide with the scarcity of resources for tuberculosis control activities. This is the case especially with respect to the provision of drugs, and supervision of services with integrated actions necessary to maintain case finding and assure compliance with treatment. As a result the reported incidence, although high, is much lower than the real incidence. In addition, interruption of treatment for lack of drugs or abandonment by patients produces a large number of drug-resistant cases which survive a long time and contribute to maintenance of the transmission chain. Changes in incidence in these countries are basically due to variations in case finding intensity and completeness of registration. This is observed especially in Haiti.

In spite of the limitations described, mortality seems to be decreasing continuously in most countries, reflecting gradual improvements in treatment and, in general, in the quality of the tuberculosis program and the health care systems in the Region (Figure 2).

The age distribution of tuberculosis incidence rates illustrates another aspect of the problem (Figure 3). Although the magnitude of the rate depends greatly on diagnostic coverage, it shows the risk accumulated in countries by age cohorts. In developed countries incidence increases in proportion to age, as a result of risk accumulated over a lifetime, and exposure to greater risks in prior decades. In developing countries the risk of infection is high and the "pool" of uninfected is rapidly exhausted, which explains the peak incidence of disease among young adults. In Venezuela the curve by age is similar to that of a developed country, whereas in Argentina there is still a peak among the young. In Venezuela the older age groups were exposed to greater risks than in Argentina, but that situation has been reversed in the last 40 years. In Chile the curve by age is changing; the risk is high but has rapidly diminished in recent years.

Figure 3. Reported incidence of tuberculosis (per 100,000 population) by age-groups in Argentina (1984), Chile (1980 and 1982) and Venezuela (1984).



Conclusions

Appropriate analysis of the data on incidence and mortality, accompanied whenever possible by information on the risk of tuberculosis infection or the prevalence of infection among children, allows measurement of the long-term result of tuberculosis control measures as well as the effect of nonspecific factors, including socioeconomic development and development of the health care system. For most of Latin America, levels of annual reductions close to those of developed countries of the Region have been achieved through organized control programs. The average reduction is estimated at 6% annually at the very least, which would reduce real rates by half in 11 years and the absolute number of cases in 18 years. These estimates refer to real incidence, since observed incidence depends on operational factors and will probably increase as coverage of the program improves and new diagnostic methods become available. A real increase in many countries is also possible, if HIV infection spreads rapidly.

Given that data interpretation should lead to program improvement and should be made in relation to programs, PAHO/WHO has assigned priority for next year to developing a system of evaluation of

program operations through periodic information from countries, similar to that already existing for epidemiological information. The basis for this system will be discussed, in November 1987, by a working group which will propose basic indicators on coverage and quality of interventions—BCG vaccines, case finding and treatment—and criteria to assess strategies, resources and intermediate activities for national and international use.

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(*Source*: Tuberculosis, Maternal and Child Health Program, PAHO.)

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TUBERCULOSIS CONTROL - CURRENT SITUATION SUMMARY OF THE VIEWS OF WORKERS INVOLVED IN TUBERCULOSIS CONTROL PROGRAMMES THROUGHOUT THE WORLD[1]

by

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[1] Background paper presented at the Study Group on Tuberculosis Control, a Joint IUAT/WHO Meeting, Geneva, 14-18 September 1981 (document WHO/IUAT/JSG/BP/81.1)

1. INTRODUCTION

The ninth report of the 1974 WHO Expert Committee on Tuberculosis[1] reviewed the current tuberculosis control measures, particularly in developing countries. Specific recommendations were made for the utilization of the technical methods available in the diagnostic, curative and preventive fields in the development of effective national tuberculosis programmes. It was emphasized that the formulation of a control programme should be guided by a clear understanding of the epidemiological, operational, economic and social aspects of the local situation. Many of the conclusions of this report are still valid and alterations to the main recommendations of the report in the light of present knowledge are in emphasis rather than radical change. The one outstanding advance is the general introduction of rifampicin and the development of short-course chemotherapy.

Tuberculosis still remains a major health problem in all developing countries, the estimated annual incidence of the disease is 200 cases per 100 000 inhabitants with the prevalence usually twice as high. Even in many developed countries the annual case load in the older age groups is considerable and tuberculosis and its sequelae remain important causes of death.

Since the report of the Expert Committee, advances have been made in the epidemiological, case-finding and chemotherapeutic fields. Furthermore, with the increasing attention paid to primary health care, culminating in the international conference at Alma Ata in 1978[2], further emphasis has been laid on the necessity of integrating national tuberculosis programmes with the general health services. In the light of these advances and changes in emphasis the centenary of the anniversary of the discovery of the tubercle bacillus by Robert Koch has been taken as an opportunity to review the tuberculosis situation.

The present paper summarizes the views of workers throughout the world who are involved in tuberculosis control programmes. It reviews the technical advances made in the last decade and their influence on the tuberculosis control measures recommended in the ninth report. It examines the development of measures to control pulmonary tuberculosis, particularly in developing countries, and the integration of the programme into the national health services. It assesses the impact of the programme on the tuberculosis situation and identifies the difficulties encountered in its implementation.

2. EPIDEMIOLOGY

To provide an idea of the magnitude of the tuberculosis problem and its trend it is customary to resort to epidemiological indices and health statistics. A matter to be considered is how well such indicators actually reflect the problem.

Annual tuberculosis infection rate

The annual tuberculosis infection rate is derived from the results of tuberculin tests in representative samples of unvaccinated subjects[3]. It is generally agreed that this rate is the best single indicator for evaluating the tuberculosis situation and its trend within the community. It expresses the attacking force of tuberculosis within the population and although highly relevant to developed countries it is particularly useful in developing countries, where, unlike mortality and notification rates, it is not directly linked with the availability and accuracy of local statistics and can be established much more reliably than the incidence of smear-positive cases.

The risk of tuberculosis infection indicates the proportion of the population which will be primarily infected (or reinfected in those who have been previously infected) with tubercle bacilli in the course of one year, and it is expressed as a percentage or as a rate. The estimated annual risk of tuberculosis infection in most developed countries is of the order of 1 to 3 per 1000. In contrast, in the developing countries it ranges from 1% to 5%. It has been demonstrated that there is an almost constant ratio between the risk of infection and incidence of smear-positive tuberculosis and it has been calculated

that in developing countries a 1% annual risk of tuberculosis infection corresponds to about 50 smear-positive cases per 100 000 general population. For the three billion people living at present (1982) in developing countries there are four to five million highly infectious cases at a conservative estimate developing each year and 2 to 2.25 million deaths from tuberculosis.

To estimate the trend of the annual risk of infection several tuberculin surveys are required at intervals (e.g. of five years), each in a representative sample of non-BCG vaccinated subjects of the same age and tested by the same technique. Information on trends has been collected in a number of high-prevalence and low-prevalence countries. It has been established that in some low-prevalence countries, where as many as 75% to 80% of the population are uninfected with the tubercle bacillus, the risk of infection is decreasing by approximately 11-13% per annum. In contrast in many of the higher prevalence countries there has been no evidence of any appreciable change or only a slow decrease in the annual risk over a number of years.

It is clear that, even when there is very little transmission of infection in children and young adults, a substantial case-load of new infectious cases may occur in the older age groups. It is also clear that estimates of the tuberculous infection rate are difficult or impossible in areas with a very high BCG coverage in infants.

Notification of tuberculosis

When the population is adequately covered by the health services, annual notification of new cases, relapses and deaths may provide good indications of the tuberculosis problem. Such was the situation in many developed countries in the first half of this century. Even today, morbidity data for developed countries still give a fair picture of the situation, though when tuberculosis becomes rare underdiagnosis and undernotification occur. Indeed, an increasing percentage of patients is not being diagnosed until autopsy. A variety of criteria for diagnosis and reporting are being used, so that comparisons between countries cannot easily be made; in particular, information on bacteriological confirmation, which would afford comparability, is generally deficient. As for mortality data, these largely lost their significance when chemotherapy was introduced, and with tuberculosis occurring more and more at old age they become less accurate, many patients dying with tuberculosis being notified as dying of tuberculosis. Surveys of the notification system can provide important information for they can identify ambiguities and inaccuracies in the system (e.g. duplicated notifications, changes in diagnosis, notifications after death) and can reveal important epidemiological differences in the pattern of the disease (for instance between ethnic groups, areas, etc.)

These shortcomings of notifications obviously also apply to developing countries, but with the added drawback that many cases may remain undetected and thus unnotified. Indeed in many developing countries as many as three-quarters of all smear-positive cases remain undiagnosed and in most the majority of cases positive by culture only cannot be diagnosed because of lack of culture facilities. It is evident, therefore, that the notification of new cases of tuberculosis is largely incomplete. A gradual improvement in case-finding of smear-positive cases may be expected in the developing countries and as it is gradually extended it is hoped that the majority of cases with symptoms will be diagnosed and treated. In these circumstances the number of cases identified will be gradually increased and notifications will then provide a more reliable yardstick of the tuberculosis problem and its trend.

Newly registered cases of tuberculosis for different years, by WHO regions, are shown in Table 1. In any one year well over one million new cases were reported, which is only a small fraction of the estimated number of new cases but already a considerable case-load. There is a lack of consistency in the reporting of new cases in almost all WHO regions, so that no meaningful comparison can be made.

In the developed countries the incidence of tuberculosis in children is low because of the greatly reduced risk of infection. In developing countries, however, this age group is still at a high risk, but since case-finding is usually based on sputum examination of persons with symptoms, tuberculosis in children may pass unnoticed since it is often not detectable in this way. Notifications for men were higher than for women (58% and 42% respectively). This tendency has been confirmed in prevalence surveys.

Deaths from tuberculosis for different years are given in Table 2. The apparent decrease is largely due to the data from the developed countries only, since they are predominant among the reporting countries. In the developing countries the death toll of tuberculosis must be many times higher than suggested by the figures presented. Still, even the reported data are most disquieting considering that tuberculosis is easily treated.

3. THE IMPACT OF CONTROL MEASURES

The technical measures available for the control of tuberculosis are case-finding combined with treatment, BCG vaccination, and preventive treatment. The impact which these measures may have on the tuberculosis situation can only be estimated for countries where the relevant data are available.

The impact of case-finding and treatment can reliably be assessed in countries where a reasonable knowledge of the "natural" trend of tuberculosis has been obtained, no mass BCG vaccination was carried out, case-finding has been intensive for many years and treatment has been nearly 100% successful in the whole population. It was possible to estimate in these conditions that the annual decrease is of the order of 12% to 13%, of which 4% to 5% is due to the natural downward trend prior to chemotherapy and 7% to 8% to intensive case-finding and effective treatment of all diagnosed cases, with and without bacteriological confirmation[4].

A sudden elimination of the sources of infection, with the introduction of chemotherapy, should have brought about a large reduction in the risk of infection in a short period of time, followed by a gradual decrease. This, however, was not observed, the probable explanation being that the level of the risk of infection was already low and the implementation of effective chemotherapy gradual. Thus, the decline must have been chiefly due to the result of active case-finding. Of particular interest is that the decline appears self-perpetuating, i.e. the decrease in the risk of infection causes a reduction in the number of sources of infection and vice-versa. If elimination of the sources of infection would merely affect the uninfected population, its impact would only be observed after a long period of time. However, the effect seems to be much wider, for it has been observed in several developed countries, where even now the large majority of elderly people is infected, that the incidence among them also declined with the risk of infection. Moreover, in England it was shown that over the last 25 years there has been more than a ten-fold decrease in the incidence of tuberculosis among tuberculin-positive adolescents. This suggests that, unless the risk of infection is extremely low, disease is to a large extent the result of exogenous reinfection in the infected population. If this were so, a reduction of the infectious pool would be of benefit to the entire population. It would probably cause an immediate reduction in the incidence of infectious, smear-positive, cases in the higher age-groups, and thus a self-perpetuating decline of the tuberculosis problem. This has been verified among the Eskimo population, in which an intensive programme resulted in a sharp decline in all age groups. Tuberculosis control strategies in developing countries should be reviewed in this light.

In many developing countries the case-finding and treatment measures carried out are unsatisfactory. It has been estimated that only about a quarter of smear positive cases are known to the treatment services and therefore there is considerable room for improvement in case-finding. Even a 30% to 50% improvement in the identification of smear-positive cases and their treatment would considerably increase the impact of control measures on the overall tuberculosis situation.

As regards chemotherapy, it has been estimated that the success rate in programme conditions from potentially highly effective regimens prescribed for one year may be of the order of 60% to 65%, with a fatality rate of 10% to 15%, resulting in a residue of about 25% of chronic bacillary excretors. The most important reason for this high failure rate is in the large number of patients who stop treatment prematurely and/or are irregular in the self-administration of their drugs. This is principally the result of a failure in the careful supervision which is required to ensure that the patients actually receive their chemotherapy. Substantially reducing the period for which patients have to be treated by using short-course chemotherapy may thus have a considerable impact on the tuberculosis situation. Short-course regimens are likely to be more acceptable to patients and will allow the staff more time, than would otherwise be the case, to devote to the supervision of patients for the relatively short period of treatment. Further, even if patients default before completing the "short" course, it is known that as high a proportion as 80% of smear-positive patients can be cured with as little as three months intensive, supervised treatment.

The question is what might be the rate of decline in the risk of infection if the minimum programme of case-finding by microscopy and one-year standard chemotherapy were implemented adequately on a national scale. The application of these measures no doubt eliminates sources of infection, but the question of how far this reduced transmission of infection is difficult to answer in developing countries.

In connexion with the objective of the programme aimed at reducing the human suffering caused by tuberculosis, young children benefit less than adults from such diagnosis and treatment programmes since child tuberculosis may pass almost unnoticed because children rarely produce bacteriologically positive sputum. Serious forms of childhood tuberculosis, such as miliary tuberculosis and tuberculous meningitis, often will be undetected or detected too late for treatment to be effective. The need for preventing tuberculosis by vaccination in young children is therefore particularly cogent.

BCG vaccination will directly reduce the incidence of disease, its effectiveness being the product of the actual efficacy of the vaccination and the vaccination coverage. In the general population the impact will be limited since BCG vaccination is only applicable in the non-infected population.

Whereas BCG vaccination may prevent very serious forms of tuberculosis such as tuberculous meningitis and miliary tuberculosis, it will prevent only a very small proportion of cases of smear-positive pulmonary tuberculosis. This form, which is the main source of infection, is relatively rare in children and adolescents. Consequently BCG vaccination, certainly when given to the newborn, will not substantially influence the chain of transmission, especially if the risk of tuberculous infection is high and has not been decreasing. Since in most developing countries the prevalence of infection in the older age groups is high, the vast majority of new smear-positive cases among the general population cannot be prevented by mass vaccination. Systematic vaccination of infants and revaccination later in life might only have an effect in the older age-groups after a long period of time.

Providing preventive treatment to healthy persons who are likely to become tuberculosis patients if not treated, would be an effective way of both preventing suffering and reducing transmission. Antituberculosis treatment is attended with certain undesirable side effects, the risk of which, however, is small. In the treatment of patients, therefore, the disadvantages largely outweigh the benefits, and most side effects are reversible if detected in time, which is likely when treatment is supervised. The matter is different when treatment is given as a preventive measure.

At the centre of the problem is that most new cases of infectious tuberculosis do not emanate from an easily recognized population at risk; so-called "high-risk" groups do not contribute more than a small proportion of all new cases in developing countries. For preventive treatment to be effective as a control measure, therefore, it would have to be administered on a mass scale to large populations at a relatively low risk. The cost of

such a programme would be high, and the incidence of side reactions would further increase the cost/benefit ratio. For these reasons mass preventive treatment is clearly unsuitable for tuberculosis control and the statement made in the report of the ninth WHO Expert Committee that "preventive treatment was not suitable for mass application in a community health programme" is still true for developing and probably for developed countries.

In developed countries preventive treatment has a role to play in tuberculosis control, particularly in certain high risk groups, for example infected contacts or silicotics. Even in developing countries with great financial resources there could be a place for selective chemoprophylaxis. It should, however, be clear that the case-finding/treatment programme has absolute priority.

4. CASE-FINDING AND TREATMENT

The object of tuberculosis control is to break the chain of transmission of infection. The most efficient way of doing this is to detect the sources of infection as early as possible and render them non-infectious by chemotherapy.

Case finding

Case-finding is not an end to itself but is a preliminary to treatment and cure. It is a crucial part in the tuberculosis control programme; however, it is important that expansion of a case-finding programme does not proceed ahead of the ability of the service to deliver effective chemotherapy and to cure the cases found.

Diagnosis of cases. Bacteriology plays a key role in diagnosing new cases of tuberculosis (and, of course, in the control of their chemotherapy). The demonstration of tubercle bacilli is conclusive and with few exceptions is necessary to establish the tuberculous aetiology of abnormalities found on chest radiographs. Radiographic appearances are subject to wide observer variation and if used as the sole criterion for diagnosis result in a substantial proportion of persons being unnecessarily treated. In developing countries radiography can only play a subsidiary role in the routine diagnosis and management of pulmonary tuberculosis because it is costly in terms of staff and equipment, and is not readily available to the majority of the population. However, it is still used in some of these countries where as many as half of the adult cases being treated for pulmonary tuberculosis are diagnosed by radiographic means only. In economically favoured countries radiography is a most useful ancillary to bacteriological examination, particularly and is indispensable for identifying active cases of pulmonary tuberculosis who are bacteriologically negative and who may become positive if not treated.

The bacteriological methods used are direct smear and culture, usually of the sputum, followed by identification of the mycobacteria and tests of sensitivity to antituberculosis drugs. In developed countries these facilities are universally utilized but priorities have to be set for developing countries. Examination of direct smears is of first importance, since it is relatively simple, not costly and detects those cases of pulmonary tuberculosis which are the most infectious. It has been estimated[3] that each smear positive case whilst undiagnosed infects at least one person per month. When smear examinations are carried out in small, multipurpose laboratories, bright field microscopy using the Ziehl-Neelsen (ZN) method should be used since capital costs are low and the technique fairly easy. However in specialized laboratories with a large flow of specimens (more than about 20 a day) fluorescence microscopy is advisable because it is efficient, quicker and ultimately less costly.

Although the identification of the most infectious smear-positive cases in the community is a first priority, examination by culture is a useful examination for it will increase the number of cases found and identify cases in a less advanced state of disease. The Expert Committee recommended that in developing countries "culture services should be provided only when a reasonably high proportion of the smear-positive cases in the country are being discovered and treated by chemotherapy". However, there is currently some difference of opinion in emphasis and it is now increasingly felt that even in the absence

of a fully satisfactory smear service, there is a need for culture facilities not only at a central level but in some laboratories at an intermediate level.

Sensitivity tests are mainly of value in developing countries for epidemiological and surveillance purposes and normally should be carried out only at the central specialized laboratory. Routine sensitivity tests at the start of treatment in patients who have not had previous chemotherapy impose an unrealistic burden on the laboratory services and can seldom be justified by the benefit they confer. However where more advanced bacteriological facilities are available, in a few developing and all developed countries, they are useful in deciding on a suitable drug regimen for patients who have failed on chemotherapy.

The tuberculin test has virtually lost its use in the diagnosis of tuberculosis in view of the widespread BCG vaccination of infants and children, but can still prove useful in areas where BCG vaccination has not been done on a wide scale and in certain individual circumstances.

In developed countries, where the incidence of genuine infection due to atypical mycobacteria is almost ten times that in developing countries bacteriological identification tests are of crucial importance in the diagnosis of atypical infections.

For extra-pulmonary tuberculosis the use of radiography and histological facilities are frequently required. The development of a specific serological test would be particularly useful in the diagnosis of extra-pulmonary tuberculosis and might also prove helpful in pulmonary disease.

Methods of case-finding. In the majority of low-prevalence countries, where treatment services are highly developed and effective, case-finding programmes, based on bacteriological and radiographic examinations, may have a high priority particularly in high risk groups such as immigrants, foreign workers, and among old persons in homes and hostels and in jails.

In developing countries the great majority of cases are identified when they present themselves at health facilities often with far advanced tuberculosis and in a highly infectious state. This passive method of case-finding yields only about a quarter of the smear-positive cases in the community and in order that there should be any impact on the tuberculosis situation more active case-finding measures to identify the large number of undiagnosed cases need to be pursued.

The only active case-finding measure used on a large scale in the past has been mass miniature radiography (MMR) but this has been virtually abandoned, except in certain high risk groups in developed countries, largely because it contributes a very limited number of infectious cases and is very expensive. It has been estimated that the cost of detecting a smear-positive case through mobile MMR examination of the general population is about 50 times higher than identification of a case by the examination of sputum smears from symptomatic patients attending health facilities. However, there are still a few countries where mobile mass radiography is currently being carried out at regular intervals.

In view of the fact that it was generally believed that tuberculosis patients failed to attend for treatment at health units, there has been an increasing interest in recent years in actively searching in the community for "tuberculosis suspects" who have chronic respiratory symptoms (a cough for one month or more) and examining them bacteriologically by smear (or by smear and culture). Several methods of identifying such tuberculosis suspects in the community have been investigated in Kenya. It was found that the proportion of suspects with a chronic cough in the general population was 5.0%, (not dissimilar to the 4.1% reported from Uganda[4], 3.5% from Upper Volta[5], 6.6% from Burma[6] and 3.6% from Indonesia[7]). The most productive of the methods investigated, which yielded 70% of the total estimated number of smear-positive cases and 65% of all culture-positive cases in the area, was a time-consuming and cumbersome procedure of interrogating household heads for suspects living in the household. This involved house-to-house visiting and is usually impractical to undertake on a large scale in the great majority of developing countries, although it is practised in Korea.

A much more practical and manageable method was interrogation of community elders on several separate occasions for suspects within their communities (containing about 1000 persons) which produced 43% of all smear-positive and 40% of all culture-positive cases but which contained a high proportion of previously treated cases. This suggested that the elders knew and remembered old cases but were less aware of subjects with common symptoms such as a chronic cough.

These studies raised the question of whether actively searching for suspects in the community was necessary at all for, surprisingly, over three-quarters of the tuberculosis suspects claimed that during the previous year they had attended one or more peripheral health units for their respiratory symptoms on at least one occasion, and the great majority on several occasions. In these circumstances it was possible that the problem was to ensure that suspects who presented themselves with chronic respiratory symptoms to these units were appropriately examined. Further studies in the peripheral health units in different districts confirmed this finding and demonstrated a singular failure of the staff of these units to initiate appropriate action for the patients or even to refer them for examination to the district hospital in spite of special efforts to encourage them to do so. The indications from most developing countries are that the failure of the staff is widespread and can be attributed to the fact that they are not highly trained or motivated, there is little supervision of their functions, their workload is considerable, they have many important acute medical and surgical priorities (malaria, dysenteries, infectious diseases, trauma) and any special procedure, however simple, is an increase to their burden.

There was additional evidence from these studies that suspects who failed to obtain relief at the periphery, then attended the better staffed and better equipped district hospital. Accordingly, a series of further investigations were undertaken involving the screening of outpatients for suspects in several district hospitals. This is relatively easily organized for there are better resources available, namely on-the-spot facilities for microscopic and radiographic examination and often a chest clinic with better trained staff to make a diagnosis and initiate treatment. This approach was encouraging and productive, for the proportion of suspects with a chronic cough among outpatients aged six years or more was 2.7% and the yield of smear-positive cases from them was 2% to 5%, whereas the yield from suspects obtained by actively searching in the community on a house-to-house basis in the same district was 1%. Similar findings have been reported from other developing countries which indicate that the proportion of suspects screened from outpatients attending health facilities ranges from 2% to 10% and the yield of cases from 1% to 10%.

The approach through the district hospital outpatients is, however, unlikely to provide by itself full coverage of the community. This presents a dilemma for to obtain full coverage of the population some activities must also be carried out in the periphery. The best methods to be employed have yet to be determined but it does mean that the staff at the periphery must be better motivated to remember to take the trouble to identify tuberculosis suspects and arrange for the examination of their sputum.

A further case-finding method investigated was the examination of all cases of pulmonary tuberculosis registered over a period of several years in the District Tuberculosis Register. It is easy to undertake (provided the register is well maintained and contains a full address for each patient) and entails the tracing and examination of only a relatively few persons. It was found to be a good way of identifying chronic excretors of resistant bacilli in the community, over three-quarters of the bacteriologically positive patients having strains resistant to isoniazid; however, less than one-fifth had strains resistant to streptomycin. The examination of their contacts was almost wholly unproductive but it might be useful if contacts of newly diagnosed smear-positive cases were examined.

A useful approach to case-finding, being evaluated in Hong Kong, has been to increase the awareness of the medical profession, of all cadres of medical staff and of the community (by a publicity campaign, posters, television and radio) of the importance of chronic symptoms referrable to the respiratory system.

In most populations in developing and developed countries, there are individuals and groups for whom the risk of tuberculous infection and disease are greater than for others. The identification of these groups is particularly important because it is more economical and more operationally feasible to concentrate case-finding efforts on them. An important high priority group is the contacts of smear-positive cases, others are health staff exposed to infection in wards and laboratories, patients who have had tuberculosis and have been inadequately treated or persons with radiographic abnormalities in the lung, especially if these are large and recently detected. Particularly relevant to developed countries are migrant groups, elderly subjects and patients with special concomitant diseases (such as diabetes, pulmonary chest diseases, silicotics and patients on steroids).

In summary, it is concluded that the present methods of case-finding in developing countries are generally unsatisfactory and produce only about a quarter of the smear-positive cases in the community. Greater attention needs to be paid to the identification of symptomatics in the community and among outpatients and the examination of their sputum. It has been demonstrated that if carried out systematically, an active policy in the community is potentially capable of identifying two-thirds of all smear-positive patients in the population.

Chemotherapy

The Ninth report of the WHO Expert Committee emphasized the importance of giving adequate chemotherapy free of charge to every patient with infectious pulmonary tuberculosis. Certain general principles were formulated, namely that patients should be treated on an ambulatory basis with careful supervision to ensure the regular administration of drugs for a year and that the benefits of prolonging chemotherapy beyond a year were small. In selecting regimens to be used, consideration should be given to the relative efficiency, toxicity, acceptability and cost of the drugs. These principles are equally relevant seven years later.

The main drugs for national tuberculosis programmes available in 1974 were isoniazid, streptomycin, p-aminosalicyclic acid (PAS) and thioacetazone. Recommended for general use in national tuberculosis programmes was the combination of isoniazid (300 mg) and thioacetazone (150 mg) in one daily dose for patients weighing 35 kg or more, an effective, inexpensive (Table 3) and widely used regimen for those countries in which the level of toxicity is acceptable. Streptomycin is frequently administered daily for the first month or two of treatment. Recommended for those countries where fully supervised intermittent chemotherapy is feasible, and carrying the benefit of overcoming undetected irregularity, was a highly effective twice-weekly combination of streptomycin (1 g or 0.75 g) plus isoniazid (in a single dose of approximately 15 mg per kg body weight) given together twice a week; with 5-10 mg of pyridoxine to prevent peripheral neuritis. It was, however, recognized that there was a need for fully oral standard intermittent regimens which could be administered under supervision by non-medical auxiliary health workers. It should be recognized that the figures for the efficacy of the various regimens shown in Table 3 are based on the results of controlled studies and are optimal results, and, in practice, frequently fall far short of these.

A review of the current methods employed for the treatment of tuberculosis in the developed countries shows that isoniazid, rifampicin, streptomycin, ethambutol and pyrazinamide are used in various combinations, often for periods of nine months or less. In many countries some, and sometimes all the patients are still being treated initially in hospital for periods up to three months and sometimes even for considerably longer.

In developing countries patients are often treated on an ambulatory basis from the start of chemotherapy, but often the first month or two is spent in hospital to cover the period during which streptomycin is given. Usually treatment is prescribed for one year but in some countries it is standard procedure to prescribe it for as long as 18 months and occasionally for two years. The standard regimen in many countries is the combination of isoniazid and thioacetazone, often with the addition of streptomycin for an initial period

of one to three months. However in other countries, where thioacetazone is unacceptable because of its incidence of side effects, it has been replaced as a companion drug to isoniazid by PAS (Na) or ethambutol. In a few countries fully supervised intermittent chemotherapy is standard treatment and in a few others short-course chemotherapy with isoniazid, rifampicin, streptomycin and pyrazinamide for six months has recently been introduced.

Short course chemotherapy. Since the report of the Expert Committee in 1974 there have been major advances in chemotherapy. The introduction of rifampicin and the recognition of pyrazinamide as an important bactericidal drug has led to the introduction of short-course regimens. Short-course chemotherapy[8,9] was primarily developed to shorten the length of standard 12-month treatment because of the difficulties, particularly in developing countries, of maintaining patients on regular treatment for one year or more. The short-course regimens have a mode of action which differ essentially from that of the other conventional standard length regimens. In standard chemotherapy it was necessary to select companion drugs for isoniazid which would prevent the emergence of drug resistance, such as thioacetazone, PAS and ethambutol - drugs with a bacteriostatic action. In short-course chemotherapy the aim is to select combinations of bactericidal drugs which are rapidly sterilizing, namely rifampicin, pyrazinamide, isoniazid and streptomycin and thereby producing a more rapid cure.

It has been shown in a series of controlled studies that a six month regimen of a combination of isoniazid (300 mg), rifampicin (450-600 mg) plus streptomycin (1 g) for an intensive phase of two months (2SHR) followed by a 4-month continuation phase of isoniazid plus rifampicin (HR) is a highly effective regimen in smear-positive pulmonary tuberculosis (Table 3). The addition of pyrazinamide (1.5 - 2.0 g) to the initial 2-month phase (2SHRZ) considerably potentiated the efficacy of the regimen. High levels of success were achieved when this 4-drug combination for two months was followed in the continuation phase for periods of four or of six months by a combination of (a) streptomycin (1 g), isoniazid (15 mg/kg) and pyrazinamide (3-4 g) given twice-weekly ($S_2H_2Z_2$), or (b) thioacetazone (150 mg) plus isoniazid (300 mg) given daily (TH). In both these regimens the expensive drug, rifampicin, was given only for the first two months, a major economy in drug cost. If the 4-drug initial intensive phase were reduced from two months to one month (1SHRZ) thus reducing the cost and the duration of daily streptomycin injections, the efficacy of the regimen was correspondingly reduced by about 10% for each of the six month and eight month regimens, respectively (Table 3).

Studies investigating even shorter courses of chemotherapy, namely 4-month regimens, with an initial 2-month phase of streptomycin, isoniazid, rifampicin and pyrazinamide (2SHRZ) followed in the continuation phase by isoniazid in combination with rifampicin and/or pyrazinamide have proved to be disappointing in smear-positive disease.

Short-course chemotherapy has several advantages over courses of standard length; the total delivery of health services is curtailed for the patients and thus more efforts can be concentrated on ensuring regular patient attendance and regular administration of drugs; the total quantity of drug used is less and therefore there is less toxicity than if the drug were given for longer periods and the cost is lower, and because of the early sterilizing effect of the drugs in the initial phase of treatment, patients who abscond early are less likely to relapse than on standard regimens.

Intermittent chemotherapy. With the introduction of rifampicin there have been further advances in regimens for supervised intermittent chemotherapy. A fully oral twice-weekly regimen of rifampicin (600 mg) plus isoniazid in high dosage (15 mg/kg) has been investigated. The regimen given for one year, was preceded by a short daily phase of the two drugs given in conventional dosage plus streptomycin for two weeks and was found to be highly effective (Table 3). The same regimen given once-weekly was also very promising and required only 64 doses in the year. Immunologically adverse reactions to rifampicin (the "flu" syndrome) were very uncommon in these regimens.

Intermittent regimens have been shown to be highly effective also in short-course chemotherapy. In Hong Kong, a fully supervised regimen of streptomycin (1 g), rifampicin (600 mg), isoniazid (15 mg/kg) and pyrazinamide (2-2.5 g) given together three times a week for four months and followed by twice-weekly streptomycin plus isoniazid plus pyrazinamide (3-4 g) for a further two months, was found to have a high success rate and when the twice-weekly regimen was given in the continuation phase for four months instead of two, the efficacy was increased to virtually 100%. Indeed, in Hong Kong, a regimen of streptomycin (1 g) plus isoniazid (15 mg/kg) plus pyrazinamide (2-2.5 g) three times a week for nine months cured 95% of the patients.

Cost of the drug regimens. In considering the applicability of chemotherapy, cost is an important factor affecting the choice. For some short-course regimens the cost is principally due to rifampicin but pyrazinamide is also a relatively expensive drug. There is a surprisingly wide variation in the price difference of a drug in different parts of the world even when it is marketed by one company (Table 4). These differences are irrespective of costs of transportation and distribution. Nevertheless, it should be recognized that the actual cost of drugs does not necessarily reflect the total cost of administering a regimen. There are other important considerations indirectly affecting the cost of treatment, namely its acceptability to patients, toxicity, whether it requires injections and its ability to sterilize lesions rapidly and thus ensure a substantial cure rate in persons defaulting from treatment early.

In developed countries, where the cost of drugs is not of such great importance (although it may be by no means a negligible factor), it seems likely that, on the basis of current findings, 6-9 month regimens containing rifampicin, isoniazid and pyrazinamide will be used for patients with smear-positive disease. For those patients negative on smear but positive on culture the duration of treatment with these drugs may be anything from four to six months and for those who are consistently negative on smear and culture (about half the patients coming under treatment) it could be three months or perhaps even two. However, the time periods for patients with smear-negative disease need further clarification.

If, however, the cost of drugs is an important consideration as in developing countries, then short-course regimens will be given only to smear-positive patients. The period for which rifampicin and pyrazinamide are administered will have to be restricted to as short an initial phase as possible and the choice for the continuation phase may well be the relatively cheap standard combination of isoniazid plus thioacetazone or possibly isoniazid alone. If on the other hand there is the ability to organize full supervision, the choice might well be a fully supervised twice-weekly regimen for the continuation phase. It is however necessary for each country to decide its own policy of chemotherapy and which regimens are appropriate, maybe in different parts of the country, to its programme conditions.

Retreatment regimens. The need for retreatment should be avoided as far as possible by making every effort to ensure the highest standards of primary treatment. In general drugs for retreatment are available only in small quantities in the developing countries. Traditional retreatment regimens containing ethionamide and cycloserine are expensive and toxic and usually require hospital treatment. In countries where the resources permit, rifampicin and ethambutol are the drugs most commonly used. A very important factor to be considered in the use of short-course regimens for primary treatment is that relapses which occur, will usually occur with organisms fully sensitive to the drugs administered and that the patients can be effectively retreated with the same combination of drugs.

Preventive treatment. In practice, isoniazid by itself is conventionally administered as a chemoprophylactic for a period of six months or more. However, it is possible that rifampicin administered for considerably shorter periods might prove equally as effective. A highly speculative possibility is that immunotherapy, either by itself or together with chemoprophylaxis, might prove a successful preventive treatment.

5. BCG VACCINATION

BCG vaccination was introduced in most developing countries as an emergency measure at a time when it was the only tuberculosis control method applicable on a national scale. Vaccination often started with a mass campaign to cover the entire eligible - tuberculin negative - population, which was followed in many countries by an integrated programme, to keep up with the birth rate. More recently BCG vaccination has been included in the expanded programme on immunization, which aims at reaching a high coverage in the lowest age group, either by vaccinating the newborn, in countries where deliveries take place mainly in institutions, or by intensive efforts through child welfare clinics and primary health care services to reach the young infants.

Direct vaccination with freeze-dried vaccine by the intradermal method is the normal procedure and coverage in the various age groups and in different countries varies widely ranging from 30% to over 90%.

In developed countries special attention was given to providing BCG vaccination before adolescence, alone or by revaccination in cases where vaccination of the newborn was also practised. In many of these countries the risk of infection had become low, and childhood tuberculosis relatively rare; adolescents and young adults appeared the group most susceptible to developing tuberculosis.

The protective effect of BCG vaccination remained a matter of controversy. The information obtained in the newborn and young children appeared very favourable, but results in adolescents and adults obtained in a series of carefully planned and executed controlled trials were contradictory. The results of the latest BCG trial in south India obviously weigh heavily in the balance. The trial was carefully designed and took account of all technological developments and results of research on BCG vaccination carried out in the previous twenty years. The complete absence of a protective effect has prompted a reappraisal of the mechanism of protection afforded by BCG[10]. There is no suggestion that the trial methodology, nutrition, freeze-drying or quality or strain of vaccine used had any influence on the efficiency of vaccination in the south India study.

The first explanation that comes to mind is sensitization with environmental mycobacteria. Indeed in the trial area this kind of sensitization was massive, but one would have expected that it might have caused a reduction in the protective effect of BCG vaccination, not a complete elimination.

In the trial area a high prevalence of tuberculosis infection appeared to be accompanied by an unexpectedly low incidence of bacteriologically confirmed tuberculosis among those recently infected. In contrast, the incidence among those already infected, particularly among adult men, was exceptionally high. The lack of protection from BCG might be related to this unusual epidemiological pattern. The pattern observed possibly could be explained from infection in the area being predominantly with a "south Indian variant" of the tubercle bacillus. This variant, first studied some 20 years ago, had been found in some 75% of the isolates from patients in Madras. It has several unusual characteristics, a striking one being that it is of low virulence in the guinea pig, unlike the ordinary tubercle bacillus. It has therefore been suggested that the organism may be fully infectious but may only rarely lead to disease soon after infection, though it might cause disease later.

The tuberculin sensitivity induced by BCG vaccination in the trial population appeared to have waned considerably within a few years. This may point to an unusual immune response. Further indications of this are the unexpected age dependence of tuberculosis as well as the high incidence of leprosy in the trial area.

Another hypothesis is that the low effectiveness of BCG vaccination observed in south India could be the result of the disease diagnosed being predominantly of the exogenous superinfection type. Whereas BCG vaccination may protect uninfected persons against primary and evolutive tuberculosis, as well as against endogenous reactivation, it cannot be expected to protect uninfected persons if their eventual disease were of the exogenous reinfection type: at the time of reinfection the level of immunity would be that derived from the primary infection, whether BCG had been given before this or not, so that controls and vaccinated subjects would have the same risk of disease from exogenous reinfection.

A study group on BCG vaccination policies[11] considered whether modifications were to be made in current BCG vaccination policies in the light of present knowledge. It was stressed that the Indian trial was not designed to establish the effect of BCG in infants and young children. The evidence available on the effect of BCG vaccination in these age groups is very favourable. Some hypotheses that explain the lack of effect in older age groups, such as a high prevalence of infection with environmental mycobacteria, do not apply to infants.

In practice BCG vaccination is being applied most often in the newborn and young infants, and this policy is being adopted more and more with the introduction of the expanded programme on immunization. There are no reasons to modify this current policy, but its effectiveness should of course be studied forthwith. Every effort should be made to identify the local factors that apparently may modify the outcome of BCG vaccination. Due attention should continue to be paid to the quality of the vaccine, its handling, techniques of application, training of personnel, coverage of population, evaluation and monitoring the programme as suggested in the ninth report of the WHO Expert Committee.

6. THE NATIONAL TUBERCULOSIS PROGRAMME

The national tuberculosis programme is a methodical approach within the country health programme designed to reduce progressively the tuberculosis problem in the community by working through the network of existing general health service institutions forming the primary health care system. The essential components of the programme are case-finding with effective treatment of the cases found and immunization of the vulnerable population.

This concept, which is current WHO policy on tuberculosis control was formulated in the ninth report in 1974.

Organization of the national tuberculosis programme

The main recommendations in the 1974 report were:

1. The programme should be permanent, organized on a country-wide basis (serving the rural equally with the urban areas), be a well-balanced component of the country health programme, integrated into the community health structure, meet the public demand and be accessible, available and convenient for the consumer rather than for those providing the services.

2. The plan of action should clearly enumerate the main events and the activities required to achieve them in their logical sequence. There should be a systematic planning of operational steps for implementation, monitoring and evaluation of the tuberculosis programme which should be based on demographical information, the system of administration and communications, the structure and coverage of the health services and the availability of manpower and resources at the central, intermediate and peripheral levels.

3. Diagnosis and treatment should be carried out by suitably trained staff operating from a network of permanent health services including outpatient departments of hospitals, health centres, dispensaries and health posts. These should be located so that all persons have reasonable access to a health-unit of some sort.

4. For implementation of the programme there should be a single strong directing authority at the central level under the Ministry of Health which should be responsible for policy making, planning coordination, training, direction and evaluation. Managerial teams, specially trained in the technical and operational aspects of the programme should play a key role and be responsible for the implementation of the programme; they should spend much of their time in the field supervising the activities and on-the-job training of the field workers, particularly at the peripheral level. Their other activities should include the organization of the distribution of equipment and supplies, and the technical evaluation of the programme components based on simple, effective and meaningful recording and reporting systems which should provide information for future planning.

5. Adequate training for all categories of health personnel emphasizing the community aspects of tuberculosis. Members of the managerial teams should, in principle, be trained as a group at a national centre and particular importance should be paid to management technology, not necessarily limited to tuberculosis. Basic information on national tuberculosis programmes should be added to the curricula of medical, para-medical and nursing schools.

Current situation of tuberculosis control programmes

In many developing countries there is little integration of the tuberculosis programme with the general health services in the capital city or very large towns. At this level there is often a considerable degree of specialization in the form of tuberculosis specialists, tuberculosis clinics, a tuberculosis laboratory and beds for cases of tuberculosis. At the intermediate level specialized clinics may exist, sometimes in the form of general chest clinics, and at the periphery in the primary health centres and sub-centres, tuberculosis patients are normally managed and treated in the general health services.

The process of integration is proceeding with varied success, but many countries are having major problems in the organization of their programmes. This is particularly true when attempts are made to integrate an already existing specialized tuberculosis service into the general health services, for such a move is usually resisted by all categories of health personnel. The specialized tuberculosis staff having limited confidence in the ability of the general service staff to master the techniques properly and the latter showing a degree of reluctance to undertake it because of the extra work involved.

Sometimes the planning of the programme is inadequate at the central level. Key personnel trained abroad may fail to implement the programme on their return with the result that there is little or no central planning and a lack of support from the Ministry of Health; directions from the centre are vague and ill defined resulting in confusion and minimal activity at the lower levels. However, frequently there is a degree of policy-making, planning and programming at the centre but this is often negated by a general weakness of the infrastructure due to the scarcity and frequent turnover of staff at all levels, an inadequate number of health units which may be poorly distributed and thus inaccessible to large sections of the population. Irregularity of the supply of drugs and equipment is common and almost invariably there is a shortage of funds resulting in a serious restriction of transport and travelling which is so necessary for the essential work of supervision and evaluation.

Often the failure at the intermediate level is due to the absence or ineffectiveness of managerial teams under the overall supervision of the general duty medical officer. It is necessary for them to be better trained as multipurpose teams in the detailed planning and managerial aspects of the programme and to have more support from the centre particularly in the provision of transport and allowances to enable them to travel and undertake the supervision and evaluation which is crucial to success.

The improvement of the managerial teams should in turn lead to improvement at the peripheral level where often the rural health staff are untrained or improperly trained, infrequently if ever supervised and often show lack of interest and enthusiasm. Technological skills can readily be acquired by health workers in the general health service but due to lack of training, poor communication with the intermediate level, shortage of chemicals, equipment and drugs and breakdown of vehicles, their motivation is frequently blunted. The ready availability of drugs and supplies is essential but frequently fails to be achieved for many and sometimes complex reasons and its rectification presents a managerial and planning challenge.

In many developed countries tuberculosis control activities are based on an independent sub-system in the health service, in others specialized tuberculosis units continue to provide specific activities but administratively they are incorporated in general health services and in a few others the activities are fully integrated into the general health services. The reason for the retention of the specialized services in these countries is the belief in them that specialized experience is necessary for the treatment of tuberculosis. Further, owing to the decline of the disease there is a generally decreasing interest in it. Tuberculosis, however, still presents a problem in the majority of developed countries and there is a need for comprehensive surveillance surveys to follow the trends in notifications, the types and severity of the disease, the management of patients and to observe the extent that clinical practice keeps abreast with modern developments (e.g. in chemotherapy).

The organization of laboratory services in the programme

In the great majority of developing countries there is normally a central laboratory, situated in the capital city, which undertakes smear and culture examinations and sometimes sensitivity testing also. In the development of the laboratory service at the central level the first step is to upgrade the quality of work at the central laboratory so that it can efficiently undertake smear examination by fluorescence microscopy and culture examinations. Sensitivity testing should only be introduced when sufficient skill and equipment is available and should be restricted to the central laboratory. At present there is difficulty in producing a high class culture service and, in those laboratories where it is done, sensitivity testing.

The central laboratory should also play an important part in the planning of the national programme, have representation on and close participation with the central management team, undertake training of technicians, be responsible for equipment specifications and for quality control of bacteriological work throughout the country. It should be a centre for epidemiological studies and should undertake research primarily aimed at solving practical problems within the country.

As the service develops, it is visualized that there will be an increase in the number of multipurpose intermediate laboratories capable of doing cultures as a specialized section within a larger general laboratory.

The first priority in the bacteriological facilities for a developing country is the provision of a country-wide service for the examination of direct smears of sputum. At present facilities for the examination of sputum smears are usually available in the general laboratories at intermediate level; if they are not, they should be made so. There are certain advantages in locating microscopes in the more peripheral areas because sputum smears can then be examined on the spot and the necessity of transporting sputum in containers, or fixed smears for examination, to the hospital is avoided. The disadvantages lie in the regular maintenance of microscopes, the training and supervision of the microscopists and the maintenance of a regular supply of staining reagents and slides. The balance of advantages between these two approaches is uncertain but it is unwise to assume that the same solution applies with equal force to all countries or to all regions in any one country.

It is evident that at present, progress to be made is mainly of an organizational nature. It is important that at the central level there is a well trained laboratory worker, motivated to serve the needs of the country and to work closely with an effective central management team which should include a chest physician and representatives from the laboratory service and the Ministry of Health. It is of the greatest importance to ensure a regular supply of slides, stains and facilities for maintenance of equipment, particularly the microscopes.

Training is important but should not concentrate wholly on teaching the technical performance of certain tests (for instance how to examine a sputum smear). Of equal importance is to teach peripheral microscopists the proper use and maintenance of the microscope, including minor repairs. An additional requirement will be for one or more workshops capable of microscope repairs which may be part of a department carrying out a wide range of repairs of laboratory equipment.

Quality control is most important and should be the function of the central laboratory. Experience in developed countries suggests that the most efficient way is for the central laboratory to send out to participating laboratories prepared specimens or smears with known contents of tubercle bacilli which are then examined and reported back to the central laboratory. This however requires skilled and dedicated personnel. A small number of developing countries have a monitoring system whereby all known positive smears and a sample of negative slides from the intermediate and peripheral laboratories are viewed centrally on a regular basis. This is a satisfactory method provided it does not unduly stretch the resources of the central laboratory and that appropriate action is taken routinely to notify the results to the participating laboratories. However, the best and most practical method of undertaking this work will have to depend on local circumstances.

Evaluation of the programme

Evaluation of the programme differs considerably from country to country but in the vast majority it cannot be said to be satisfactory. In a few countries evaluation is carried out by managerial teams or other supervisory staff but only on a limited scale because of shortage of staff and transport facilities. Sometimes the programme is evaluated through routine statistical returns received from the periphery indicating the number of cases treated in various areas. Occasionally national and regional seminars are organized at which the programme is discussed. Although the need for evaluation of the programme is recognized, its implementation suffers due to shortage of trained staff and financial resources and poor communication between the centre and periphery.

A useful form of evaluating national programmes is by nationwide surveys of cohorts of patients coming under treatment which can provide much useful information on the epidemiological situation. Thus, they will indicate the types of tuberculosis being treated, the methods of diagnosis employed, the drug sensitivity pattern, the types of treatment given, the outcome of treatment, including the defaulter rate, mortality and ultimate bacteriological status of the patients.

Tuberculosis registers. In developing countries, the "notification" of cases of tuberculosis on a national basis frequently depends on a system of registration in tuberculosis registers of cases of tuberculosis coming under treatment. These registers are often maintained at an intermediate level and perform a most important function in tuberculosis control. The aim should be for them to be simple and provide essential information, including age and sex of the patient, the site of the disease, the method of diagnosis (bacteriological, radiographic, histological, clinical) and the exact address so that the patient can be contacted readily. They should also provide a cross reference to the individual case cards detailing the treatment of the patients and the management of their families. Apart from providing information for the national statistics the registers provide an essential guide in the surveillance of the anti-tuberculosis activities within each area, in relation to the site of the disease, the method of diagnosis, the initial treatment and the areas in which the patients live.

Economics

A tuberculosis programme requires special resources, even if integrated in the general health services. As tuberculosis is a disease against which a highly efficient technology exists the position is favourable in competing for resources with other health demands. However, because comparison between the importance of different diseases in the community is very often based on subjective considerations, the decisions on allocation of resources will also remain highly subjective.

A balance has to be found in the antituberculosis programme between curative (case-finding/treatment) and preventive (BCG vaccination) services.

Chemotherapy is essential for the control of the disease and consideration has to be given to the relative cost of drug regimens. Cheaper regimens with lower individual efficiency under programme conditions may prove expensive in the long run. Thus, they may result in a large number of unsuccessfully treated patients who may still be infective to others and who are in need of retreatment with more expensive drugs probably for considerable periods in hospital. However, there is no objective final formula which will take into account the large number of factors involved.

The economics of tuberculosis control in relation to integration will behave differently according to the degree of integration of health services. The balance is between the trade-off between technical knowledge (presumed to be higher in a specialized system) and the advantages in lower cost and continuous care afforded by the integrated system. To become efficient, integration requires a basic infrastructure into which to integrate and this is frequently non-existent or too weak, and must be strengthened before it can become economically advantageous.

7. PRINCIPAL REASONS FOR FAILURES IN THE NATIONAL TUBERCULOSIS CONTROL PROGRAMME

The failure of a national tuberculosis programme can be broadly defined as a failure achieve a decrease in the tuberculosis problem in the country over a number of years. This can be said to have occurred in the majority of developing countries. In a few, mainly those with considerable financial resources, there has been a decrease in the problem. In the economically favoured developed countries there has been a marked success in the control of the diseases over the period of the last half century, which has been achieved because of the full availability of technical and financial resources and in spite of mistakes, sometimes serious, which have been made. The present document attempts to summarize the main reasons for the failure of national programmes in the developed countries.

The fundamental reasons for failure are the lack of financial resources and manpower. Failures, directly or indirectly resulting from these can be broadly identified under the following headings:

7.1 Planning of the programme

a) A lack of planning or ineffective planning of a country-wide programme is usually due to a lack of interest of control key staff which results in the absence of strong managerial teams at the Ministry level, with a wide and comprehensive membership, to carry the plans into effect.

b) A deficiency or absence of epidemiological data in the country on which to base a plan.

c) A failure of planning and coordination at the intermediate level, often due to the non-involvement of the district medical officer and the absence of a managerial team.

d) Because of the absence of support, supervision and proper instruction the peripheral staff are left to carry on as best they can.

e) The absence of managerial teams, or the failure to provide facilities for travel when they exist, leads to a lack of technical guidance, supervision and training at all levels.

7.2 Staff

a) Doctors, specially trained to organize control programmes frequently have an undue clinical bias and find it more satisfying to treat patients than to organize a countrywide programme.

b) Staff responsible for organizing the programme may lack the full support of the Ministry of Health when it comes to the implications of launching or maintaining the programme.

c) There is a disinclination by the central organizing staff to devolve responsibility because of their limited confidence in the ability of the general service staff to master the techniques properly.

d) The general health service staff are most reluctant, without extra help, to increase their work-load by being involved in other more chronic conditions, requiring extra time and expertise. They have many priorities, particularly acute conditions demanding immediate attention (e.g. trauma, pneumonia, malaria, acute surgical emergencies, etc.)

e) The staff at the periphery are poorly trained and lack adequate supervision.

f) All grades of general health service staff are subject to frequent postings, often with little notice.

g) There is a great lack of organized training schemes for all grades of staff and of on-the-spot training, particularly for staff at the periphery.

7.3 Transport

a) There is a general lack of vehicles and often those that are available are immobilized because of lack of spare parts and/or breakdowns. There is almost universal lack of proper maintenance for vehicles particularly at the intermediate and peripheral levels.

b) Because of the escalating price of oil, the use of vehicles has to be severely restricted.

c) There is often insufficient planning in the optimal use of transport enabling a variety of functions to be undertaken in one journey rather than several separate journeys.

d) The use of pedal cycles and motor bicycles in place of cars is frequently impossible in the rough conditions of rural areas.

e) In the absence of vehicles, funds required for travelling (e.g. by public transport) and living expenses for supervisory staff are frequently totally inadequate.

7.4 Supply of drugs, vaccines and equipment

a) Because of difficulties in the transport system, and often because of poor organization, supplies of drugs, chemicals, vaccines and equipment are allowed to run out without being replaced for considerable periods. This results in frustration of the medical and paramedical staff and disenchantment of the population with the health services.

b) Often "time-expired" drugs and vaccines are being used.

c) Occasionally anti-tuberculosis drugs, and sometimes diagnostic procedures are charged for.

7.5 Distribution of health facilities

Peripheral health facilities are often insufficient in number, and those that do exist are inaccessible or situated long distances from large sections of the population.

7.6 Referral services

a) The use of supportive referral services between the various levels is greatly hampered, particularly at the peripheral level, by lack of transport and adequate road communications.

b) There is often confusion and misunderstanding by patients being referred by private practitioners, and mission hospitals to government institutions and vice versa.

7.7 Bacteriological services

a) There is a lack of well qualified and motivated staff to plan the expansion of the bacteriological service, and to create a liaison with the clinical services which is crucial.

b) The regular supply of chemicals to laboratories and the maintenance of equipment, particularly microscopes, is frequently defective.

c) More supervision of laboratories at the intermediate and peripheral levels, including an effective monitoring service, is required.

7.8. Case-finding

a) There is a general lack of sustained attempts at case-finding.

b) The identification and appropriate examination of chronic respiratory symptomatics attending out-patient departments is not attaining its full potential, due principally to the lack of motivation and training of the staff, particularly at the peripheral level.

c) Very few active case-finding measures are being pursued in the community.

d) The examination of household contacts, of at least the smear-positive index cases, as a routine is frequently not done.

7.9 Treatment

There is a universal problem of maintaining patients on chemotherapy for a year:

a) Default and irregularity in the self-administration of the drugs is outstandingly the most important reason for failure of treatment. The identification and tracing of defaulters is hampered sometimes by the absence of an organized method of approach but more often by the scarcity of staff and transport to enable defaulting patients to be contacted, particularly in the rural areas.

b) The non-availability of drugs at the distribution points often causes irregularity in the administration of chemotherapy.

c) Inadequate instructions to the patient on the administration of drugs may lead to incorrect dosages being self-administered.

d) The transfer of patients during their treatment from one area to another can lead to interruption and possibly cessation of treatment unless standard procedure for such transfers is laid down.

e) Toxicity of the drugs may cause interruptions of chemotherapy and staff are frequently unaware of the necessity for it to be dealt with urgently in order to avoid frequent irregularities in the administration of drugs.

7.10 Evaluation and surveillance

a) Because of the absence or of the failure of managerial teams to function properly there is inadequate routine supervision and surveillance at all levels.

b) This results in the irregular and insufficient collection of statistics necessary to evaluate the programme.

c) Periodic country-wide surveys of cohorts of patients coming under treatment to evaluate the programme, including the results of chemotherapy, are undertaken in only a very few countries.

d) There is a need for more countries to maintain adequate registers of all patients coming under treatment.

e) The countries require to undertake estimates of BCG coverage through vaccination returns and scar surveys.

8. RESEARCH

It is relatively easy to specify the broad areas in which research in tuberculosis is important, but more difficult to qualify the specific activities which should be pursued. These have been set out in detail in a recent report on research on tuberculosis by a Committee of the British Medical Council[20]. Taken as a world problem the priority for research must be to help the developing countries improve the performance of their national tuberculosis programmes and thereby reduce the incidence of the disease.

There is little doubt that the main problem in the national programmes of developing countries lies in the organization of the programme. The first priority is for more operations research to find simpler and more acceptable methods of administration and organization (including methods of decentralization and integration). Of equal priority is to conduct research into methods to improve training, including motivation of all grades of staff in case-finding and case-holding. These may seem mundane and unimpressive research projects, but they are of crucial importance to the improvement of the national health programmes.

Very efficient potential control technology already exists for tuberculosis and the implementation of this has led to a remarkable reduction in the incidence of the disease in developed countries. However, in order to simplify the organization of the tuberculosis control programme in developing countries further research into methods of control is needed. Thus, there is a need for a simple test, possibly serological, which can be used clinically and epidemiologically, for diagnosing active tuberculosis in a quantitative and qualitative manner, particularly for diagnosing tuberculosis in children and extra-pulmonary forms of the disease. Better methods of case-finding both active and passive (including research into methods of motivating staff, particularly at the periphery) require investigation in different countries and different situations. In the field of chemotherapy, it is most important to find simple and effective methods of preventing default (e.g. use of community leaders) and there remains a need for research into new drugs and regimens for further shortening the length of chemotherapy and to assess the efficacy of short-course regimens in programme conditions. For preventive measures, there is a requirement for a more effective and possibly oral vaccine.

In the epidemiological field there is a need for a more specific tuberculin test or other methodological approach so that the impact of the control measures (case-finding/treatment and/or vaccination) can be measured simply and accurately.

Important other areas for research are the development of simple methods of surveillance, monitoring methods of therapy and notification by surveys, and assessing the impact that quality control schemes (e.g. of smears) have at the peripheral level. Of a more fundamental nature, but in a rapidly expanding field, is research in the immunological aspects of tuberculosis, particularly in identifying reasons for breakdown of inactive disease. Childhood tuberculosis has been particularly neglected and there is a need for more attention to be paid to research in this field.

9. LIST OF WORKING AND BACKGROUND PAPERS

V. K. Agadzi	Critical review of the application of tuberculosis control technology in primary health care WHO/IUAT/JSG/WP/81.4
P. Cavalié	Solutions to some problems facing integrated tuberculosis control programmes in developing countries WHO/IUAT/JSG/BP/81.5
P. Chaulet	Applicability of short-course chemotherapy to the national tuberculosis control programmes of the developing countries WHO/IUAT/JSG/WP/81.7
G. Dahlstrom	Identification of problems requiring further research if they are to be solved WHO/IUAT/JSG/WP/81.25
S. Endo	Comments on current tuberculosis control policy WHO/IUAT/JSG/WP/81.4
A. F. Farah	Tuberculosis control and primary health care services WHO/IUAT/JSG/WP/81.13
L. S. Farer	The problem of high prevalence groups in low prevalence countries WHO/IUAT/JSG/WP/81.10
L. S. Farer	The role of preventive treatment (chemoprophylaxis) in tuberculosis control WHO/IUAT/JSG/WP/81.19
J. Grosset	Changes and advances in current technology for the bacteriological diagnosis of tuberculosis WHO/IUAT/JSG/WP/81.2
F. Luelmo	Critical review of the application of tuberculosis control technology in primary health care WHO/IUAT/JSG/BP/81.3
P. Mercenier	Operational problems encountered in the implementation of tuberculosis control programmes and need for health services research to solve them WHO/IUAT/JSG/WP/81.23
D. A. Mitchison	Organization of tuberculosis laboratory services in developing countries WHO/IUAT/JSG/WP/81.3

D. R. Nagpaul	Why integrated tuberculosis programmes have not succeeded as per expectations in many developing countries - a collection of observations WHO/IUAT/JSG/BP/81.4
S. J. Nkinda	Critical review of the application of tuberculosis control technology in primary health care WHO/IUAT/JSG/WP/81.11
W. P. Ott	Critical review of the application of tuberculosis control technology in primary health care WHO/IUAT/JSG/WP/81.12
K. S. Sanjivi	Can tuberculosis be eradicated through primary health care? WHO/IUAT/JSG/BP/81.2
T. Shimao	A review of case-finding methods and problems of delay in case-finding WHO/IUAT/JSG/WP/81.9
H. Stott	Centralization and decentralization of case-finding activities for pulmonary tuberculosis at district level in Kenya WHO/IUAT/JSG/WP/81.8
K. Styblo	The present epidemiological situation of tuberculosis in developing countries WHO/IUAT/JSG/WP/81.1
K. Styblo	Epidemiology of tuberculosis in children WHO/IUAT/JSG/WP/81.20
TRI Unit WHO, Geneva	The role of BCG vaccination in tuberculosis control programmes WHO/IUAT/JSG/WP/81.15
TRI Unit WHO, Geneva	Tuberculosis control - a world summary WHO/IUAT/JSG/BP/81.9
H. Th. Waaler	Tuberculosis and economics WHO/IUAT/JSG/WP/81.21

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11. ACKNOWLEDGMENT

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TABLE 1

Newly registered tuberculosis cases by WHO Regions
1965 - 1970 - 1975 - 1979
- All forms -

Year and WHO Region	Reporting countries		Newly registered cases
	Number	Population - in thousands	
1965			
Africa	33	141 283	157 822
Americas	40	366 087	183 544
Eastern Mediterranean	12	89 045	76 469
Europe	23	388 056	311 802
South-East Asia	1	11 164	13 112
Western Pacific	12	196 642	509 258
Total	126	1 192 277	1 252 007
1970			
Africa	36	222 672	196 316
Americas	38	499 124	202 834
Eastern Mediterranean	15	138 584	108 648
Europe	24	430 737	358 885
South-East Asia	2	48 259	45 439
Western Pacific	22	213 693	404 564
Total	137	1 553 069	1 316 686
1975			
Africa	30	170 658	68 044
Americas	42	553 074	178 140
Eastern Mediterranean	17	201 956	184 601
Europe	25	493 526	208 089
South-East Asia	5	821 629	551 669
Western Pacific	21	195 305	279 867
Total	140	2 436 148	1 470 410
1979			
Africa	17	150 253	54 064
Americas	41	597 233	164 466
Eastern Mediterranean	11	139 335	149 891
Europe	20	399 181	141 312
South-East Asia	3	875 097	559 395
Western Pacific	16	157 920	100 390
Total	108	2 319 019	1 169 518

TABLE 2

Deaths from tuberculosis in the world
1965 - 1970 - 1975 - 1979
- all forms -

Year	Reporting countries		Officially reported deaths
	No. of countries	Population - in thousands (%of world population)	
1965	116	1 223 808 (36.6%)	178 213
1970	134	1 488 900 (40.5%)	156 880
1975	112	1 426 245 (35.5%)	121 634
1979	61	1 001 894 (23.1%)	53 545

TABLE 3

The effectiveness in controlled studies of some standard and short-course regimens and their cost

Regimen	Duration of regimen and potential efficacy (%)				Duration of regimen and cost (US$) to UNICEF*			
	1 year	9 months	8 months	6 months	1 year	9 months	8 months	6 months
1 STH/TH	95	-	-	-	8	-	-	-
1 SPH/PH	95	-	-	-	73	-	-	-
S_2H_2	90	-	-	-	14	-	-	-
1 STH/S_2H_2	95	-	-	-	18	-	-	-
2 SHR/HR	-	100	-	95	-	191	-	130
2 SHRZ/HR	-	-	-	99	-	-	-	140
2 SHRZ/TH	-	-	100	90	-	-	60	59
2 SHRZ/$S_2H_2Z_2$	-	-	100	90	-	-	82	74
1 SHRZ/TH	-	-	90	80	-	-	33	31
1 SHRZ/$S_2H_2Z_2$	-	-	98	90	-	-	57	48
4 $S_3H_3Z_3$/$S_2H_2Z_2$	-	-	99	95	-	-	37	29
1 HR/H_2R_2	100	-	-	-	81	-	-	-
1 HR/H_1R_1	95	-	-	-	46	-	-	-
$S_3H_3Z_3$	-	95	-	75	-	52	-	44

S = streptomycin; P = PAS; H = isoniazid; R = rifampicin; Z = pyrazinamide; TH = thioacetazone
The number preceding a set of letters is the number of months of the intensive phase; the continuation regimen follows the stroke (/).
For intermittent regimens the number of doses per week is shown by the suffixed numbers.
*The cost of the drugs is based on current prices to UNICEF and includes a 30% handling and freight charge.
The cost of the regimens is calculated for an adult weighing less than 50 kg and is expressed to the nearest dollar.

TABLE 4

The varying cost of drug regimens

Therapeutic regimen	Length of treatment	Cost in U.S. dollars				
		Latin America[15] 1979	Algeria[15] 1980	UNICEF* 1981	U.K. 1978	U.K.** 1980
1STH/H	12	13	7.5	8	10	27
1STH/S_2H_2	12	30	12	17	20	64
2SHRZ/RH	6	183	167	161	273	393
2SHRZ/TH	6	91	70	59	103	159
	8	92	71	60	104	161
2SHRZ/$S_2H_2Z_2$	6	119	91	74	129	203

The UNICEF and U.K. prices have been calculated for an adult weighing less than 50 kg and expressed to the nearest dollar.

* The UNICEF prices include 30% handling and freight costs. The price of pyrazinamide is that quoted to WHO by the manufacturers

** The conversion from sterling to dollars has been based on an average exchange rate during 1980 of US$ 2.3 to £1 (Bank of England quote).

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TREATMENT OF TUBERCULOSIS:

CASE HOLDING UNTIL CURE

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A. INTRODUCTION

For the national tuberculosis programme, the final objective of treatment is not only to deliver adequate chemotherapy to every newly discovered infectious case but also to take all possible measures to ensure proper drug dosage, regularity of drug intake and adequate duration of treatment, to achieve the patient's cure. In order to achieve this goal, technical guidelines must be available that have correct and locally adapted answers to the following eight questions:

a) Who are the patients that should be admitted to treatment?
b) Which is the place of treatment?
c) Which therapeutic regimen to apply?
d) How to organize a regular supply and distribution of drugs?
e) How to ensure treatment compliance of individual patients?
f) How to arrange for treatment follow-up?
g) How to organize the supervision of all treatment activities?
h) How to evaluate the results of treatment within a national tuberculosis programme?

In addition, there are two problems that can arise and which need specific but transitory decisions to be taken:

i) How to implement a modern policy of tuberculosis treatment in a situation of organizational anarchy? Or how to modify a current practice of inappropriate treatment?
j) In a well organized and standardized tuberculosis programme, how to introduce new regimens of chemotherapy that are different in composition and duration from the ones in use?

B. TREATMENT GROUPS

1. The two main groups with absolute priority for treatment are:

   - sputum smear positive, pulmonary tuberculosis cases (actual sources of infection)
   - smear negative but culture positive, pulmonary tuberculosis cases (potential sources of infection).

These two groups are responsible for the transmission of the infection and the perpetuation of the disease in the community; they represent from 70 to 80% of tuberculosis cases, all forms. Without treatment, half of the smear positive cases would die within two to three years.

2. The subsidiary treatment groups that should be treated according to the means available are:

   a) The few acute tuberculosis cases without bacteriological confirmation (febrile acute miliary disease and tuberculous meningitis)

   b) Smear (and culture) negative pulmonary tuberculosis, which can only be diagnosed through X-ray examination.

   - In children with pulmonary lesions, whether isolated or associated with mediastinal or pleural lesions, frequently the sputum examination by microscopy is negative. Childhood tuberculosis is mainly found among the contacts of an active source of infection.

   - Among the adults, on the contrary, these cases should be precisely defined under two situations:

     - If culture facilities are not available, smear negative pulmonary tuberculosis, defined as those cases that had two series (from four to six specimens each) of negative smears, are treated only if there is highly suggestive evidence of progressive tuberculosis on chest X-ray.

- If cultures are performed, treatment is justified only when there are signs of radiological deterioration for 2-4 weeks before culture results are available.

(c) Cases of extrapulmonary tuberculosis, identified on the basis of clinical signs (tuberculous lymphadenitis, tuberculous pleurisy or ascitis) or radiological signs (osteo-articular or urogenital tuberculosis) and a positive reaction to tuberculin, with or without bacteriological or histopathological confirmation (according to the type of laboratories which are available).

C. PLACE OF TREATMENT

It has been established beyond any doubt that success in the treatment of tuberculosis depends neither on duration of hospitalization nor on rest and special diet but that it is function of quality and duration of chemotherapy. Domiciliary/ambulatory chemotherapy, regularly delivered, not only gives equally good results as chemotherapy delivered in hospitals or sanatoria but also is sociologically more acceptable to patients because it does not disrupt their normal life. Finally, isolation of a patient in a hospital bed does not necessarily reduce the risk of contagion to the contacts, since transmission of infection within the household takes place mostly before the diagnosis. Home is the ideal place for treatment, even if it is in a slum or favelas, or is a nomadic tent, because this is most acceptable to the patient, since it interferes less with his work and his family life.

It is simpler and more practical to organize domiciliary treatment than hospitalization for a long period and for all the patients, and it is far less expensive so that with the amount of money needed to treat one patient in a hospital, six to ten patients can be treated domiciliarily.

1. The most important problem is to organize health services able to deliver permanently adequate chemotherapy. This can be achieved through:

   (a) either the organization of delivery of chemotherapy in the patient's home,

   (b) or the organization of services for the administration of chemotherapy to patients at the basic health units, dispensaries or health centres. These health units must be easily accessible to the patients, clean, open for service daily, and able to deal with patients with sympathy and consideration. They must deliver:

   - either fully supervised treatment (daily or intermittent), the drugs being taken by the patient under the direct supervision of health personnel

   - or treatment which is partly supervised (during the first phase) and partly self-administered by the patient (during the second phase of treatment). Self-administration of the drugs depends upon the active participation of the patient in his own cure. His participation should be supported by a member of his family, by a community health worker and by the attention given by all health personnel to regularity of treatment.

2. A secondary problem is often put forward by doctors: the need to have enough beds for all patients who have to be hospitalized for the daily administration of drugs and the application of injections.

   The usual medical indications for hospitalization are: severe haemoptysis; serious deterioration of the patient's general condition; pyopneumothorax secondary to the rupture of a pulmonary cavity through the pleura; complications of diseases associated with tuberculosis (for example, acquired immunodeficiency syndrome, and worsening of diabetes, of cardiac, hepatic or renal insufficiency); tuberculosis of the hip or spine leaving the patient unable to walk.

   Some relative indications are linked to the qualification of the health staff at peripheral level. This personnel often prefers to refer to the hospitals:

- cases of failure of domiciliary chemotherapy (real or supposed)
- relapse cases in whom a decision of a retreatment regimen should be taken
- cases with manifestations of drug toxicity requiring chemotherapy adjustments.

When there are no beds, or the existing beds are not easily accessible to patients, there is no reason to establish them. Judicious use should be made of the available beds in a planned manner under clear guidelines of the national tuberculosis programme. When hospitalization of tuberculous patients is clearly indicated, there is no reason why beds in the nearest general hospital should not be used: the old ideas on isolation of tuberculous patients should be abandoned because appropriate chemotherapy ensures that even the most infectious patients are rapidly rendered non-contagious. There is no point in sending all patients to a specialized hospital (when one exists): such a hospital is generally situated much further from the patients' homes than the general hospital, and its communication with the basic health units is more difficult or non-existent. In summary, there is no good reason why general hospital beds cannot be used for tuberculosis when indications are specified by the national control programme and if the number of patients is small.

Certain physicians bring up the question of insufficient health personnel at the periphery, and the inadequate qualification of such personnel, to justify hospitalization of all patients - particularly those from the poorest and most distant rural areas - for the initial phase of treatment. However, even when patients would accept this, it can only be a partial and temporary solution. It could not be applied in all parts of the country, due to the lack of hospitals and although it allows supervision of treatment to be made for one or two months, it does not solve the problem for the total duration of treatment. In such a situation, the efforts of the physicians would be better employed in training primary health care personnel at the periphery, rather than in persuading patients to stay in hospital for two months, far from their families.

It is not necessarily true that supervision of chemotherapy is always better organized at hospital than in domiciliary treatment. Patients, as a general rule, do not need to be hospitalized. In the long term it is more efficient to organize treatment supervision on an ambulatory basis, ensuring that the responsibility for the regular drug intake is assumed by the patient, the family and the health personnel right from the beginning of treatment.

D. CHEMOTHERAPY

Chemotherapy quickly reduces the number of bacilli present in the lesions and thus very quickly reduces the infectiousness of a patient. Because of the slow rate of multiplication of bacilli, chemotherapy must be followed for many months in order to achieve their total destruction and to prevent relapse.

1. Basic principles of good chemotherapy

The following are the main principles of good chemotherapy:

a) The patient must receive an effective drug regimen, i.e. one which has been shown in a controlled trial to be effective, is acceptable by the patient, and does not interfere with his family and social life.

b) The patient must know and accept to consume the exact dosages of each drug as prescribed. If he feels that he has a problem, he should not modify or stop treatment on his own, but must discuss it with the doctor or nurse at the health service.

c) Treatment must be uninterrupted, and the drugs must be taken very regularly, every day or three times or twice per week as the case may be. The patient should be informed that interruptions can cause failure of treatment.

d) Treatment must be taken for the full prescribed duration, one year, eight or six months as the case may be, even if the symptoms disappear within a few weeks.

In addition to the above technical principles of good chemotherapy, there are several operational ones which must also be observed in national tuberculosis programmes:

a) Only the standard drug regimens with proven efficacy must be prescribed. There is no place for tailoring the drug regimen to the needs of a particular patient or for haphazard modifications to regimens made on the spot by the personnel and not in line with the technical recommendations. This does not mean that other regimens might not be good on an individual basis but uncontrolled multiplication of regimens hinders a planned procurement and distribution of drugs. Standardization of regimens is the first requisite to permanent availability of drugs in a programme.

b) Prescribed regimens must be supplied free of charge to every patient, to ensure that treatment is not interrupted because of the inability of the patient to pay for the drugs. It is sometimes said that people do not value things that are given to them free. This is not a good argument. A large volume of evidence exists which shows that the inability for the individual patient or for the community to buy even inexpensive drugs is one of the main reasons for the interruption of treatment in developing countries.

c) Patients' convenience, and not that of staff in the health unit, is what matters most in ensuring good chemotherapy. Thus treatment organization must make sure that the chemotherapy is made available near to the patient's home; that he is contacted/visited at home whenever he does not appear in the health unit to collect the drugs; that his treatment is readily transferred to another convenient health centre when he moves home; that he is precisely informed about the new place where he should call or the name of the person whom he should contact to continue his chemotherapy.

d) Health education of the patient and his family should not be limited in time, and independent from treatment activities. It must be systematic, repeated and integrated with other activities. Welcoming, clean and accessible health clinics together with punctual, conscientious and kind health staff are very powerful factors of health education. They will ensure the patient's full and wholehearted cooperation in bringing his treatment to a successful end.

2. Essential Antituberculosis Drugs

Six essential antituberculosis drugs (Table 1) are sufficient for organizing a chemotherapy programme in any given situation:

- isoniazid and rifampicin, which are the two major bactericidal drugs
- streptomycin and pyrazinamide which have a complementary bactericidal action
- thioacetazone and ethambutol which (like PAS, in previous times) are companion drugs to the major drugs and serve to avoid emergence of drug resistance.

a) Isoniazid (H): is the most potent bactericidal drug. It is given by mouth. It is usually supplied in tablets of 100 mg and 300 mg. The therapeutic daily dose is 4-6 mg/kg body weight, both for adults and children. The total daily dose should never be more than 300 mg. This low daily amount is sufficient in both slow and rapid isoniazid-acetylators on condition that it is taken in one single dose. It is not only unnecessary but also impracticable under programme conditions to measure the serum concentration of isoniazid in order to adjust for individual treatment.

In twice weekly intermittent regimens the dosage should be increased to 12 to 15 mg/kg body weight (dosage should never exceed 15 mg/kg) in both adults and children.

Table 1

Essential antituberculosis drugs (1) and their pharmaceutical presentations

Name	Pharmaceutical presentation	Dosage
Isoniazid (H)	Tablet	100, 300 mg
Rifampicin (R)	Tablet or capsule	150, 300 mg
Pyrazinamide (Z)	Tablet	500 mg
Streptomycin (S)	Powder for injection (sulfate)	1 g
Ethambutol (E)	Tablet (chlorhydrate)	100, 400, 500 mg
Combinations		
Thioacetazone + (TH) Isoniazid	Tablet	T 50 + H 150 mg, and T 150 + H 300 mg
Rifampicin + (RH) Isoniazid	Tablet	R 150 + H 100 mg and R 300 + H 150 mg
Rifampicin + (RHZ) Isoniazid+ Pyrazinamide	Tablet	At least four different dosage combinations are available (2)

(1) The Use of Essential Drugs, WHO Technical Report Series N.722, 1985.

(2) For daily administration:

R 120 + H 50 + Z 300 mg
R 120 + H 80 + Z 250 mg
R 150 + H 75 + Z 400 mg

For intermittent administration, three times a week:

R 100 + H 125 + Z 375 mg

In daily treatment the usual dosage is 20-25 mg/kg body weight during the initial two months, and thereafter 15 mg/kg body weight. The daily dose should never exceed 1.2 g. In intermittent treatment the dosage should be adjusted to 40 mg/kg body weight for each day of treatment, without exceeding 2 g.

Intermittent treatment with ethambutol should be reserved for retreatment schemes in association with rifampicin. The association of ethambutol with isoniazid is less efficient in intermittent treatment than in daily regimens; this is why intermittent treatment with ethambutol and isoniazid is not recommended.

Ethambutol is generally better tolerated than thioacetazone but much more expensive. The main side effects are optic neuritis, diminution of visual acuity, confusion in colour vision and finally blindness. Toxicity can be detected in adults and all complications avoided by early withdrawal. Ethambutol should not be prescribed to children because it is difficult to detect in them the early signs of ocular toxicity. The dosage of ethambutol should be reduced in patients with renal failure.

f) Thioacetazone (T): is given by mouth. It is a bacteriostatic drug which is always associated with isoniazid in a fixed combination (TH), supplied in two different tablets:

- one tablet containing 300 mg isoniazid and 150 mg thioacetazone, which represents the effective daily dose for adults

- one tablet containing 100 mg isoniazid and 50 mg thioacetazone, which facilitates the adjustment of the daily dose to the patient's body weight, particularly in children.

The daily dosage is 2.5 mg/kg body weight in both adults and children. Thioacetazone should never be used in intermittent regimens.

It is well tolerated in a large number of developing countries, as has been shown in many international cooperative controlled trials. The main side effects are hypersensitivity, skin rash and digestive problems. A very severe toxic reaction that may exceptionally be seen during the initial weeks of treatment is the Stevens-Johnson syndrome or exfoliative dermatitis. This reaction may be more common in some countries than in others. Thioacetazone is safe enough, however, to be used as a companion drug in many countries.

The combination isoniazid-thioacetazone is an effective combination with the advantage of being very cheap.

The doses of the six essential antituberculosis drugs for daily and intermittent regimens are presented in Table 2.

Table 2

ESSENTIAL DRUGS AGAINST TUBERCULOSIS
Recommended dosages

Drug	Abbreviation	Daily		Intermittent	
		mg/kg	maximum mg	mg/kg	maximum mg
Isoniazid	H	5*	300	15	750
Rifampicin	R	10	600	10	600
Pyrazinamide	Z	30	2000	50 (3 times a week)	2500
				70 (2 times a week)	3500
Streptomycin	S	15	1000**	15-20	1000
Ethambutol	E	25***	1200	40	2000
Thioacetazone	T	2.5	150	--	--

* 10 in children
** 750 patients of over 50 years of age
*** 15 after two months

Table 3

SUITABLE REGIMENS OF CHEMOTHERAPY FOR TUBERCULOSIS
IN NATIONAL CONTROL PROGRAMMES (1987)

Duration in months	Regimens(1)	Failures/ relapses %	WHO drug cost(3) dollars (1987)	WHO drug cost(3) ratio (4)
12	2 STH/TH	5-10	7.2	1.0
	1 SH/SH_2	5-10	9.0	1.2
	2 SEH/EH	5-10	13.2	1.8
8	2 SRHZ/TH	0-3	31.1	4.3
	2 SRHZ/H	0-3	30.0	4.1
	2 SRHZ/SHZ_2	0-4	43.7	6.0
6	2 SRHZ/RH	0-2	69.4	9.6
	2 ERHZ/RH	0-2	67.6	9.4
	2 RHZ/RH	0-2	66.1	9.1
	2 RHZ/RH_3	0-2	43.3	6.0
	2 RHZ/RH_2	0-2	37.5	5.2

Key:

(1) The drugs utilized in these regimens are conventionally represented by the following letters: H = isoniazid, R = rifampicin, S = streptomycin, Z = pyrazinamide, T = thioacetazone, E = ethambutol.
The number preceding the first letter indicates the duration in months of the initial intensive phase; the number which follows the last letter represents the number of weekly doses in the continuation phase if the regimen is intermittent.

(2) The prices are average prices for adults, calculated on the basis of prices paid by WHO to producers in 1987. They are not the actual price of the drugs on the shelf of the pharmacy of the health unit. It is necessary to add the cost of transportation and distribution which represents an increase of 50 to 100% over the WHO price.

(3) The ratio or relative cost of regimens is based on their cost relation to the less expensive regimen, to which a value 1 was assigned.

3. Standard drug regimens

The essential drugs available today allow us to compose highly efficient chemotherapy regimens: the potential efficacy of these drug regimens, when regularly followed, is virtually 100%, as demonstrated in different controlled clinical and comparative field trials in many countries (see Table 3).

These regimens share the following characteristics:

- they have two phases: an initial intensive phase, usually of eight weeks, with three or four essential drugs and a subsequent continuation phase with generally two drugs given daily or intermittently, three or two times a week.
- they are well tolerated
- they are of low toxicity.

These drug regimens differ in two main respects: their duration (12 months for the longest and six months for the shortest regimen) and their price.

In the tuberculosis programme of a country, two alternative regimens could be adopted: one, a daily drug regimen, fully supervised during the initial intensive phase, if possible, and then self-administered in the continuation phase; the other initially daily in the intensive phase and subsequently intermittently, both phases fully supervised. These two regimens can guarantee efficient chemotherapy of all newly diagnosed patients, wherever they live (urban or rural), whatever their way of life (sedentary or nomadic), their medical problems (other diseases) or behavioural problems (psychopaths or drug addicts).

The categories of standard drug regimens based on different durations, but all highly efficient, are as follows:

3.1 Twelve-month drug regimens

The 12-month drug regimens have been widely used in the world after the 8th Report of the WHO Expert Committee on Tuberculosis, published in 1964.

All these regimens have a potential efficacy of more than 90% and over 95% if streptomycin is given daily for at least the first eight weeks. The risk of major toxicity which implies the discontinuation of at least one drug is variable but it is not higher than 4%.

These regimens are still used in many developing countries because of their low cost. Their effectiveness under programme conditions is always inferior to their potential efficacy, which entails the need for retreatment of a large proportion of patients, 20 per cent or more.

3.1.1 2STH/TH

The regimen associating 12 months of daily isoniazid and thioacetazone, with an initial supplement of daily streptomycin (from four to eight weeks), is the least expensive regimen. The association of three drugs in the initial intensive phase quickly reduces the number of bacilli and makes it useless to continue up to 18 months.

Moreover, this association considerably reduces relapses from pre-treatment drug resistance, whether primary resistance to streptomycin and/or to isoniazid, or a natural resistance to thioacetazone, which is common in West Africa, where strains of Mycobacterium africanum are prevalent.

When streptomycin cannot be given to all patients, due to financial constraints, the use of this regimen should be restricted to sputum positive cases.

3.1.2 2SEH/EH (and 2SThH/ThH)

In some countries, isoniazid and ethambutol are associated for one year in a daily regimen (ethambutol thus replacing thioacetazone). This regimen SEH/EH is comparable in efficacy to the former one: it is better tolerated but always more expensive.

In other countries, thioamides (Th = ethionamide or prothionamide) are utilized instead of thioacetazone. Wherever applied, this regimen seems efficient, but there are no controlled trials that compare the efficacy of this regimen to STH/TH: moreover, optimal daily dosages of thioamide in association with 300 mg of isoniazid are not yet clearly determined. Usually 500 mg of thioamides are prescribed as the daily dose, but some studies suggest that lower doses could be equally effective.

Tolerance to thioamides is variable in different countries, and the association of isoniazid and thioamide is always more expensive than the combination isoniazid and thioacetazone.

3.1.3 1STH/SH_2 or 1SH/SH_2

This 12-month alternative drug regimen has the advantage of being a fully supervised one and the disadvantage of having 124 to 136 intramuscular injections of streptomycin, which may not be welcome. After an initial intensive phase of daily chemotherapy, the continuation phase comprises fully supervised twice weekly isoniazid (at higher doses, 12-15 mg/kg) and streptomycin.

It is also possible to give a fully intermittent regimen (SH_2) for one year with comparable efficiency. Intermittent drug regimens with thioacetazone and isoniazid or isoniazid and ethambutol have lower efficacy and should not be used.

3.2 Nine-month regimens

The nine-month regimens - 2RHE/RH or 2 RHS/RH - have been widely used in developed countries since 1976. They are based on a daily administration of isoniazid and rifampicin during nine months, with the addition of a third drug - ethambutol or streptomycin - during the first two months. Now they are being gradually abandoned because, having the same efficacy, they are longer and more expensive than the 6-month regimens which contain pyrazinamide in the first phase.

3.3 Eight-month regimens

In the eight-month regimens, rifampicin is given only during the first two months. Therefore they are less expensive than 6-month regimens in which rifampicin is present throughout the full course. To compensate for the lack of rifampicin in the second phase a total duration of eight months is required with these regimens.

3.3.1 2SRHZ/TH or 2 SRHZ/H

This drug regimen combines in the initial intensive phase of two months (eight weeks) four essential drugs: isoniazid, rifampicin, pyrazinamide and streptomycin, daily; in the continuation phase of six months, isoniazid and thioacetazone (or isoniazid alone) are given daily. The regimen is well tolerated and has over 98% efficacy. The risk of toxicity is very low, even during the initial four-drug intensive phase. The regimen 2SRHZ/H should be used only in countries where the initial mycobacterial resistance to isoniazid is low.

The use of four drugs in the initial intensive phase makes it possible to achieve 90% culture negative results in two months: therefore drug consumption under strict supervision is imperative during this phase, whether in hospital, in the health centre or at home. The six-month continuation phase of thioacetazone and isoniazid (or isoniazid alone) is self-administered daily.

The advantages of these regimens are shortening of duration of treatment and supervision, high efficacy, low toxicity and a fairly large possibility of applicability, even in rural areas of developing countries, because of their relatively low cost.

3.3.2 2SRHZ/SHZ_2

If there is a need for a fully supervised eight-month regimen it is possible to give isoniazid, streptomycin and pyrazinamide, twice a week, during the second phase. The total duration of this regimen should be eight months, since its discontinuation after the sixth month reduces the efficacy.

3.4 Six-month regimens

These are the shortest regimens that can be applied in tuberculosis programmes. They are also the most effective regimens; their potential efficacy is more than 98%. The combination of isoniazid, rifampicin and pyrazinamide has the highest bactericidal and sterilizing activity against tubercle bacilli.

3.4.1 2RHZ/RH

This regimen is based on the association of daily isoniazid and rifampicin for six months, with the supplement of daily pyrazinamide during the first two months. The use of tablets combining the three drugs of the first phase and the two drugs of the second phase makes compliance easier to the patient, and reduces the risks of toxicity and failure due to errors in the dosage.

This regimen is effective in the treatment of pulmonary and extrapulmonary tuberculosis, in children and in adults.

If fully supervised treatment is desirable, isoniazid and rifampicin can be given either three times or two times a week during the continuation phase - regimens 2RHZ/RH_3 and 2RHZ/RH_2 -.

3.4.2 2SRHZ/RH or 2ERHZ/RH

In countries with high prevalence of initial mycobacterial drug resistance it is desirable to add a fourth drug - ethambutol or streptomycin - in the first phase of treatment of smear-positive pulmonary tuberculosis. Ethambutol is a good fourth drug choice because primary resistance to it is still quite rare. However, streptomycin is generally preferred because the need for the injection offers the best opportunity to the health personnel to fully supervise the first phase of intake of oral drugs.

In these two regimens, isoniazid and rifampicin can be administered intermittently, three or two times a week during the continuation phase. The regimens can also be administered intermittently throughout, three times a week.

4. Choice of standard drug regimens

One of the most important decisions is the choice of drug regimens to be applied in a national programme.

Many factors should be taken into consideration when taking a decision:

a. wrong prescribing habits (for example, intermittent monotherapy with daily isoniazid and streptomycin twice weekly, systematic addition of tonics and pyridoxin, too long treatments, fanciful associations) or drug consumption habits within the country (complete disregard for pyrazinamide, but widespread use of thioamides; free sale of antituberculosis drugs by chemists, even without prescription)

b. the insufficient competence in tuberculosis control of those in charge of training health personnel (medical and nursing students). The inadequate knowledge of the teachers often poses considerable obstacles to a modern policy of chemotherapy, as it contributes to perpetuating schemes which are archaic or scientifically unfounded

c. the direct or indirect influence of drug manufacturers.

This list of constraints is not exhaustive, but it shows possible causes of failure if obstacles are not removed before a good chemotherapy programme is to start.

4.1 Criteria of decision

Three objective criteria should be applied in decision-making:

a. the money which is available for antituberculosis drugs at national level

b. the number of patients to treat, taking into consideration the number of cases that can realistically be diagnosed and kept under treatment for an appropriate period.

c. the state of development of health services, present coverage of the population and level of training of health personnel who have to deliver and supervise chemotherapy at the peripheral level.

The amount of money spent on antituberculosis drugs in the country is not only the drugs budget of the public health services; one should also find out the consumption of such drugs in the private and social security systems and compare the information with national pharmaceutical production figures (when drugs are manufactured locally) and the quantities imported. The analysis of the amount spent for each of the essential or subsidiary drugs consumed in the country makes it possible to identify erroneous or excessive prescribing, to detect whether financial resources under public services that were meant for the purchase of antituberculosis drugs are being diverted to other purposes, and to determine how the available money could be spent in a wiser and more useful way. Obviously, the cost of antituberculosis drugs on the world market is an important criterion for planning a more rational policy for the purchase of drugs.

In this respect, the list of prices paid by WHO for essential drugs is a valuable indication to estimate the basic price of the drugs (price FOB, excluding transport to destination and distribution within the country) (Table 4).

Table 4

WHO PRICELIST OF ESSENTIAL ANTITUBERCULOSIS DRUGS (1987)

Drug	Form/dosage		WHO cost (US dollars)	Quantity
Isoniazid	tablets	100 mg	2.74	1000
		300 mg	4.93	1000
Rifampicin	tablets (or capsules)	150 mg	4.05	100
		300 mg	8.15	100
Isoniazid+ thioacetazone	tablets	100 + 50 mg	4.83	1000
		300 + 150 mg	10.60	1000
Isoniazid+ rifampicin	tablets (or capsules)	100 + 150 mg	N.A.	100
		150 + 300 mg	16.00	100
Pyrazinamide	tablets	500 mg	35.13	1000
Streptomycin	vials	1 g	6.00	100
		5 g	25.00	100
Ethambutol	tablets	400 mg	9.10	1000

Note: - The FOB (free on board) price of purchases ordered through WHO may be calculated by adding 3% to the price indicated above.
- The CIF (cost, insurance, freight) price is the FOB price plus the cost of transport with insurance to the purchasing country.
- To obtain the price of the drug ready for delivery to the patients, the cost of distribution within the country should be added to the CIF price.

The number of patients to be treated should be calculated as realistically as possible. If the health services cover the overall population and if the diagnostic facilities are also widely extended, the annual infection rate may be used as a direct criterion (50 to 60 new smear positive pulmonary tuberculosis cases per 100 000 population per year for each 1% of the risk of infection).

However, this relationship should be adjusted if the means for case-finding and diagnosis only allow identification of a fraction of all cases. As an indication, the reported incidence of cases diagnosed under routine conditions may be noted; if the number of cases diagnosed is really low (in relation to the estimated annual risk of infection), the principal task is to increase the coverage of the case-finding activities in order to arrive at diagnosing two thirds of the infectious cases present in the community. If two-thirds of infectious cases are identified every year, it is necessary to estimate how many comply regularly with the drug intake, how many are cured and how many need a retreatment course.

The participation of the health services in respect of treatment of tuberculosis should be evaluated according to two indicators:

- the proportion of basic health units which participate in the delivery of tuberculosis treatment;

- and, in particular, the number of auxiliary health personnel who are able to dispense the drugs distributed, to supervise the intake of drugs by the patients and to administer intramuscular injections.

In spite of the differences between regions, or between urban and rural areas within any country, it is also possible (and simpler) to use a single significant overall indicator: government health expenditure per year and per inhabitant, which is an exact indication of the public services' possibilities of maintaining an efficient health network and of paying its personnel(1).

In these basically unequal conditions of resources it is impossible to define a unique chemotherapy policy for all the countries and each country should decide on its own strategy.

4.2 A model for decision

Bearing in mind the following three criteria for decision:

- the cost of different regimens, according to their duration of twelve, eight or six months
- the number of patients to be treated
- the budget for health per year and per inhabitant

it is possible to choose a strategy for chemotherapy, using a model for decision. This model might be useful in those countries where health expenditure per year is less than 20 dollars per inhabitant (Table 5).

When the per capita expenditure is around one dollar, the 12-month regimens have to be chosen, regardless of the epidemiological situation.

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(1) According to the annual report of the World Bank in 1983, these expenses are: one dollar per year in countries with a low income (2210 million inhabitants) ten dollars per year in countries with intermediate income (1128 million inhabitants) 240 dollars per year for industrialized countries (1100 million inhabitants).

When the expenditure per capita is between two and four dollars, 12-month regimens must be used if the risk of infection is higher than 2%. But if the risk of infection is 2% or less, an eight-month regimen can be chosen.

When the per capita expenditure is between five and 10 dollars, the 12-month regimens are applicable where the risk of infection is superior to 4%; the eight-month regimen if the risk of infection is lower than 4%, the six-month regimen if the risk of infection is lower than 2%.

When the per capita expenditure for health is between 11 and 20 dollars, six-month, or eight-month regimens can be chosen, according to the epidemiological situation.

When the per capita expenditure is superior to 20 dollars, six-month regimens should be generalized and there is no reason why longer regimens should be adopted.

The model presented in Table 5 may help to decide on the national policy for chemotherapy. The current world trend is to adopt 6- or 8-month regimens because they are more effective against both sensitive and initially resistant bacilli than the 12-month regimens. The reduction in treatment failures and relapses implies a reduction in the use of retreatment drugs. Although the cost of short-course regimens is higher than that of the drugs for one-year treatment, the over-all cost for the patients, the families and the health services is lower if the duration of treatment and cure rates are taken into account. It should also be considered that in most developing countries the price of drugs for an 8-month regimen is less than the cost of four standard thorax radiographies or hospitalization for one week.

Table 5

A SIMPLIFIED MODEL OF DECISION-MAKING FOR CHOOSING
A STANDARD CHEMOTHERAPY REGIMEN IN A NATIONAL PROGRAMME
OF TUBERCULOSIS CONTROL ACCORDING TO DRUG COST AND DURATION

Annual risk of infection (%)	Governmental health expenditure per annual per capita (dollars US)				
	1	2-4	5-10	11-19	20 and more
up to 1%	does not exist	8	6	6	6
1 - 2%	12	8	6	6	6
2 - 4%	12	12	8	6	6
4 - 6%	12	12	12	8	does not exist

Key: The numbers inside the table represent the duration in months of standard chemotherapy regimens.
The duration is connected with the WHO prices in 1987 (Table 3).

12-month-regimens (2 STH/TH or 1 SH/SH_2) cost 10 dollars as an average.

8-month-regimens (2SRHZ/TH or H) cost 30 dollars.

6-month regimens (2 SRHZ/RH or RH_2) cost 40-70 dollars.

E. PERMANENT AVAILABILITY AND REGULAR DISTRIBUTION OF DRUGS

Three basic conditions should be met in order to ensure success of the chosen chemotherapy policy:

- drugs must always be available in sufficient quantity
- drugs must be distributed free of charge
- distribution of drugs to the patient must be controlled to ensure his regular supply.

1. Permanent availability of drugs

Once the decision to use standard chemotherapy has been taken and all personnel has been informed, sufficient quantities of the drugs must be made available at all levels, especially at the most peripheral health units. The financial resources necessary to purchase these drugs should be included in the regular budget of the health services in order to ensure regular supply. Relying on extrabudgetary sources for the purchase of antituberculosis drugs could result in non-integration of these drugs in the national list of essential drugs; interruption in supply if extrabudgetary aid is no longer received; outside assistance agencies (of governments or non-governmental organizations) imposing a regimen that is inappropriate or too costly for the national means; national health authorities' losing interest in a health action programme because others have taken responsibility.

The quantity of drugs can easily be calculated on the basis of the selected regimens and the number of cases to be treated. Purchase orders for one full year should be established with anticipation at all levels: peripheral, intermediate and central. The national global purchase order for antituberculosis drugs should be controlled at the central level.

Whenever possible, it is advisable that the drug purchasing system be centralized. This procedure is economical and helps in obtaining better prices. Purchasing procedures vary according to country: private dealing markets or tender procedure. Whatever the procedure, it is essential to use the generic names of drugs and not the commercial ones; to specify the exact dosage, composition and form of the active product content (sometimes it is useful to mention the colour and the different form of tablets containing the same product or the same association but at a different dosage); to foresee the necessary quantity for the needs of one year plus a security stock of 20-25% of supplementary provision of drugs over the requirements of one year. Centralized purchasing has another advantage: it offers the opportunity for quality control of drugs at the central level, using methods which are independent of those which are (or should be) applied by the manufacturers. Such quality control methods are essential in order to obtain constant guarantee of the quality and uniformity of the drugs purchased by the health services.

Central pharmacy services should be equipped in such a way that storage of drugs (to avoid deterioration) and their manipulation for transport are constantly guaranteed. A transport service using trucks, trains or even planes should be organized in order to ensure the flow of drugs from the central pharmacy to regional warehouses and from there to the rural hospitals and the periphery. The personnel of these services should be trained to control purchasing and product flow, to preserve the products from deterioration and to control and respect the expiry dates.

Each pharmacy hospital should hold a stock of drugs sufficient for three to six months (this varies according to country or the regions within the country) and distribution to the peripheral health units for all the essential drugs should be done each month or week (according to local conditions) so that all health units should regularly receive a sufficient quantity of tuberculosis drugs in proportion with the number of cases treated. The distribution of drugs to patients should be foreseen by the central services. Antituberculosis drugs should never be handed loose or in a paper bag to the patient: rain or the patient's perspiration could accidentally dissolve the drugs and render them useless. A special container (in glass, aluminium or plastic) or small plastic sachets that are easy to press shut should be supplied to all peripheral health units with the packages of drugs (boxes of 100, 1000 or 10 000 tablets).

2. Free-of-charge distribution of antituberculosis drugs

As already discussed, the free supply of antituberculosis drugs is one of the operational principles of the chemotherapy programme. This principle is easily applicable when free supply of essential drugs is ensured within the framework of a primary health care policy. It is sufficient to include in the list of essential drugs the names of the antituberculosis drugs constituting the chosen standard chemotherapy regimen.

In countries where the health system is supported by a social insurance system, it would be advisable to organize a national central purchase of drugs, rather than ask the patients to buy and be refunded later, which could lead to corrosion of the family budget and encourage patients to buy only part of the prescribed drugs. In countries where there is neither free-of-charge supply of essential drugs nor a social insurance system, health services should organize the free distribution of antituberculosis drugs themselves.

3. Regular and controlled administration of drugs to the patients

All the previously mentioned measures are indispensable but the true key to success of a chemotherapy programme is the regular and controlled administration of drugs to the patients.

During the first phase of treatment, generally eight weeks, it is essential that the daily dose be taken by the patient under the supervision of health personnel.

Drug intake can be either intermittent, fully supervised, or daily, self-administered, in the continuation phase (4, 6 or 10 months). If it is daily, self-administered, the patient must collect the drug supply at regular intervals, once a week, or every 2 or 4 weeks, which has to be clearly established from the start of treatment. Drugs should be given in closed boxes or plastic envelopes to protect them from humidity. Each box or envelope should carry a label indicating the patient's name and the exact number of tablets needed until the following collection day.

F. HOW TO ENSURE THE PATIENTS' COMPLIANCE

Once the drug distribution has been efficiently organized, the health units should ensure that the correct drugs and doses are prescribed to the patients and that the patients follow closely the given indications. Measures intended to ensure the patients' compliance should be written with the same detail as the chemotherapy regimens in the national guides on treatment of tuberculosis. The following measures should be considered:

The first contact between the patient (and a member of his family) and the doctor/health officer and nurse in charge of the supervision of treatment, is often a crucial event on which the success of treatment and the future of the patient depend. This contact should be standardized and should include a personal conversation with the patient in a language understood by him. This conversation makes it possible:

- to inform the patient about his disease, about its infectiousness and its curability; and about the choice of regimen which is available within the national programme
- to obtain the various addresses of the patient: his present home address, the address of his family (spouse and children), of his parents, relations and friends, and that of his place of work. Having these addresses makes it possible to locate him at a later date in case of absence during treatment
- to establish a list of contacts living in the same house, or same room
- to enrol him in the tuberculosis register of the health unit, to establish his individual record and to supply him with a treatment card where the date of the next appointment is clearly indicated.

During the first visit a clinical form must be filled in before treatment: weight of the patient, information on previous antituberculosis treatment, pre-existing pathologies (allergies, liver and digestive problems, psychological problems, renal function), associated pathology (diabetes, pneumoconiosis), pregnancy, and regular intake of other drugs that might interact with the antituberculosis treatment (antiepileptics, adrenal hormones, oral contraceptives, etc.). Sugar and proteins in the urine may be investigated when possible. These investigations may help to prevent toxic reactions and to adapt the chemotherapy regimen to the social and medical situation of the patient.

During the initial intensive phase, all the drugs should be given to the patient every day (or three times weekly) and he should swallow them at once (with a glass of water), under the supervision of a nurse or community health agent. This intensive phase can take place as already discussed, at home, at the health unit, or sometimes in hospital, in any place where injection of streptomycin can be applied.

It is essential that all drugs are administered each day to the patient and that the health personnel check the drug tolerance and register any complaints or toxicity reactions. Strict supervision in this phase allows corrective measures to be made in good time and helps to convince the patient of the seriousness of the treatment.

During the continuation phase, the drugs may be distributed regularly to patients in two different ways:

- For patients living within 5 km of the dispensary or health unit where the drugs are distributed, or in specific situations where complete supervision is necessary, intermittent chemotherapy regimens are often selected. The patients come for their drugs twice or three times weekly and take them under strict supervision, until the end of treatment.

- In all other cases: rural patients or those living more than 5 km from the dispensary and patients who are responsible and who have received a good health education, are handed the drugs at fixed dates, for periods of one to four weeks maximum, for a daily, self-administered treatment.

Drugs could exceptionally be given for longer periods to patients who make seasonal changes of residence, who work far from their region of origin, or who are nomads. In all these cases, daily, self-administered chemotherapy regimens are prescribed. Simple measures of health education should be taken in order to encourage the patient to take his drugs regularly: the patient and a member of his family (spouse, relation, elder brother or sister) should be informed as to the number of tablets to be swallowed each morning; the number of tablets for a given period should be counted in front of him; he should be given a container (glass, aluminium or plastic) with a screw lid, in which to protect his drugs from damp; the date of his next appointment should be given to him and marked on his treatment card. The same procedure should be followed at each appointment until the end of his treatment.

In case the patient is absent from the expected appointment, immediate action (defaulter action) should be started: home visit, convocation, visit to relatives, friends, or place of work, in order to encourage the patient to continue his treatment. This action should be started within one week after the day of absence, otherwise the neglected patient will soon be forgotten and lost sight of before the end of the treatment period. The health personnel is more responsible for the patients' compliance than the patients themselves.

Every visit the patient pays to the health unit in relation to his tuberculosis treatment should be registered on the treatment card. The patient may also carry a copy of his card.

The treatment card provides the exact information on the patients' compliance with drug intake in the supervised treatment, and with drug collection in the self-administered treatment. The control of these cards is essential to monitor the organization of domiciliary treatment.

To evaluate patient compliance other control measures have been proposed, such as unannounced visits to count the number of tablets the patient still holds, and the urine test to detect drug metabolites. These procedures are very useful in controlled clinical trials but they are expensive and are not easy to implement in national control programmes. They may also create the feeling in the patient that he is a mistrusted individual.

G. TECHNICAL MEASURES FOR THE FOLLOW-UP OF TREATMENT

When selecting the chemotherapy regimens to be applied under the national programme and the methods to ensure compliance, it is important to prepare technical instructions on the measures to be taken in order to monitor the efficacy of the treatment, to interrupt or change a treatment, and to detect and correct any undesirable effects.

1. Control of the efficacy of treatment

In cases of pulmonary tuberculosis, bacteriological examination of sputa (by microscopy at least, and by culture where possible) at appropriate intervals is far more important than periodical X-ray examination. Bacteriological examination of sputa during treatment is carried out at the microscopy (and, if possible, culture) laboratory which is nearest to the health unit where the patient collects his drugs. The sputum samples are collected at the patient's home or in the health unit and are sent the same day, whenever possible (and at the latest five days after collection), to the laboratory. Once or twice monthly bacteriological examination of sputa is optional during the first two months of treatment; if it can be done, it makes it possible to show the patient and the health personnel that the treatment is being correctly followed and that it is effective, by pointing out the progressive decrease and then the disappearance of bacilli from the samples.

In 12-month regimens, it is recommended to repeat sputum examinations at the sixth and ninth month and, in particular, at the end of treatment, at the eleventh and twelfth months. In six-month and eight-month regimens, it is recommended to carry out the bacteriological examinations of sputa one month prior to the end of treatment, and at the end of treatment (at the fifth and sixth months, or at the seventh and eighth months).

Each time, two sputum samples should be collected, if necessary the same day. If the patient is unable to produce a sample (which is frequent), he should be asked to produce the result of strongly clearing his throat after prolonged coughing. When a good chemotherapy regimen is regularly administered to and correctly taken by the patient, no bacilli are generally found in the sputum beyond the third month of treatment.

In cases of extrapulmonary tuberculosis, clinical examination (and possibly also X-ray examination) of the affected organ, after two and six months, and at the end of treatment, makes it possible to monitor the disappearance of symptoms or the appearance of scars and inactive sequelae. In cases of urinary tuberculosis, bacteriological examination of the urine should be carried out during treatment and at the end of treatment, at the same intervals as bacteriological examination of sputum in pulmonary tuberculosis.

2. Criteria to decide on the termination, resumption or change of chemotherapy

In cases of pulmonary tuberculosis, the bacteriological examinations carried out during and at the end of treatment are sufficient to allow a decision to be made.

a. If the examinations of the last two months of a regular treatment are negative, the patient should be considered cured, whatever the extent of radiological pulmonary sequelae. Treatment should be stopped. The cured patient is informed that he should consult if the respiratory symptoms recur, but systematic medical supervision after treatment is absolutely unnecessary.

b. If one of the two examinations carried out in the last two months of treatment is found to be positive, cure may be considered possible but doubtful: further sputum samples should be examined monthly for three months. If all the supplementary bacteriological examinations are negative, the patient can be considered cured. If one of the supplementary bacteriological examinations is positive, treatment failure is probable and a new treatment should be prescribed.

Treatment failure occurs when, during the regular course of treatment, the bacteriological examinations of sputum persist positive, or they become again positive after a transient period of negativity. Relapse is the emergence of positive results in the bacteriological examinations any time after the completion of a regular successful period of treatment.

In pulmonary tuberculosis the failures and relapses together should not be higher than 5 per cent with the 6-month and 8-month regimens, or 10 per cent with the 12-month regimens if all patients are correctly treated.

In cases of extrapulmonary tuberculosis, a patient is considered as cured when after a regular course of chemotherapy, there are no longer clinical, biological or radiological signs of active disease. Failures or relapses are rare.

3. The problem of retreatment

3.1 Most often this problem concerns patients who have taken their drugs irregularly or interrupted treatment prematurely. The risk of failure or relapse is high when more than 25 per cent of the prescribed doses of a determined regimen are not taken by the patient. In these cases the same chemotherapeutic regimen which was prescribed originally should be started again, under close supervision and strict monthly bacteriological control. An effort should be made to identify the social, economic, psychological, educational or organizational factors which induced the irregularity or defaulting to study whether any corrective measure can be undertaken.

3.2 Failure during regular chemotherapy is very rare. Initial resistance to isoniazid or streptomycin is the most likely cause of failure in a patient who complies with the prescribed chemotherapy regimen. Other causes can be a mistake in the dosage of the drugs (under-dosage), and the pharmacologic interaction between the tuberculosis drugs and other medicaments which the patient might be taking. If no other causes can be identified, the normal assumption is that the bacilli are resistant. If feasible a sensitivity test should be done. As a general rule, the patient should be prescribed a completely different regimen including:

- during the first three months, three drugs to which the bacilli were shown to be susceptible, or which the patient has not received before for more than three months,
- thereafter, two drugs daily or twice a week, for a continuation period of nine months.

The most effective retreatment regimens are those in which rifampicin, ethambutol and pyrazinamide are associated in the first phase (3 REZ/RE or 3 REZ/RE_2).

3.3 Relapse after a regular course of chemotherapy is rare in compliant patients. They are 5-10 times less frequent after short-course chemotherapy than after the 12-month regimens.

If relapse occurs after a 6-month regimen, the isolated bacilli are generally susceptible to the drugs. The same regimen as previously prescribed should be given again, under close supervision.

If the original regimen had an 8-month or 12-month duration, the excreted bacilli are often resistant to isoniazid at least, and many times to two drugs. A different regimen should be prescribed for a total duration of 12 months, as indicated in the preceding section about the retreatment of failures.

3.4 Repeated relapses after several, complete or incomplete, courses of chemotherapy may be caused by irregularities in drug intaking, medical errors in the prescribed regimens, or deficiencies in the organization of domiciliary treatment.

The number of "chronic " patients (those who have excreted tubercle bacilli for more than one year) is large when supervision and control of tuberculosis treatment is not well organized.

Many of these cases have received all or almost all the known antituberculosis drugs. Therefore a sensitivity test is essential to select a rational therapy.

4. Detection and correction of side effects

Technical guides should clearly state all possible side effects that can occur during treatment with the standard regimen so that health personnel should be properly informed of the corrective measures to be applied.

Preventive measures should make it possible to identify "risk" groups of patients: those who are underweight, who have a history of renal or hepatic insufficiency or of allergy, and those with proteinury. Such patients should be closely supervised, or should undergo complementary biological examinations whenever possible, with a view to adapting or adjusting the standard treatment, if necessary.

Corrective measures would depend upon the nature and seriousness of the secondary effects observed. Some side effects, such as digestive problems, are minor and do not justify stopping the treatment. Others are more serious and call for temporary or final withdrawal of one of the drugs; these normally need hospitalization and referral of the patient to a medical consultant to identify the drug responsible for the problem and to decide on the continuation of treatment. Lastly, problems which may arise due to the combination of antituberculosis drugs and other drugs which the patient may be taking (oral contraceptives, corticosteroids, oral antidiabetics, cardiac glycosides) should be considered: health personnel should be able to consult the national technical guidelines in order to find instructions for any specific situation.

H. SUPERVISION OF TREATMENT ACTIVITIES UNDER PROGRAMME CONDITIONS

1. Supervision of treatment delivered at the health unit itself is easy; it is sufficient to check that each patient whose treatment card is marked has in fact taken the number and doses of drugs prescribed on each day of his daily or intermittent treatment.

2. Supervision of drug distribution to patients collecting their drugs for self-administration is also easy. In a health unit having more than 10 patients to supervise, it may be preferable to decide on one or two days each week for the distribution of antituberculosis drugs: each patient's prescription can thus be prepared in advance, which facilitates supervision. Each time the patient collects his drugs, the quantity and the date should be noted on his treatment card and on his personal file which is kept in the health unit. Supervision consists of a weekly check on the treatment cards or on the individual files of patients under treatment.

3. It is more difficult to supervise the actual taking of drugs for self-administration in the patient's home. The essential measure is to motivate the patient or a member of the family to take the responsibility for treatment as a result of the explanations given at the beginning of treatment and renewed in each successive contact with the patient and his family. Urine tests on samples of patients may be used to evaluate compliance in the programme.

4. Any weaknesses in the distribution system should be identified and corrected; absence on the part of the patient at an appointment should result in defaulter action. Treatment supervision and defaulter action are facilitated by decentralization and by integration of tuberculosis treatment within the routine activities of the basic health services in

the most peripheral health units, as close as possible to the patient's home. With increasing decentralization, there are fewer and fewer patients who are irregular in their treatment or who default. With strong supervision of treatment activities, there are fewer errors, and omissions by the health staff, and less waste of drugs.

I. EVALUATION OF A TREATMENT PROGRAMME

Intermediate and central level evaluation of a treatment programme has two principal aspects:

- evaluation of a treatment programme during the application
- evaluation of the results of the treatment programme.

1. The basic documents for this evaluation are the register of notified tuberculosis cases (register of notifications in which all the tuberculosis cases of an area or district are registered chronologically) and the individual records of the patients in the health units.

   The information to be collected for each patient is: the name, surname, sex, age, address, health unit; the initial diagnosis (pulmonary or extrapulmonary tuberculosis), the initial bacteriological status, background or previous diagnosis and treatment of tuberculosis; prescribed chemotherapy and the starting date of treatment.
   The register can be completed at a later date for each patient, with the results of follow-up and of the bacteriological examinations carried out until the end of treatment, and an indication of the patient's condition at the end of treatment or 12 months after the start (cure, death). In a last column there should be space for any special comments (such as transfer of the patient to another health service, or early interruption of treatment).

   The patient's personal file should include all medical and social data collected before or during treatment. It should be possible to find the exact quantity of drugs received by the patient, the frequency and duration of omissions or interruptions in treatment, and the results of follow-up.

2. Evaluation of a treatment programme during application

   The simplest method is to send to the intermediate or central level each month a copy or reproduction of the pages of the register, with the information concerning the cases reported during the last month. This monthly list permits the control of the number of cases admitted to treatment, their classification by diagnostic methods, age and sex, regimens prescribed. It is thus possible to follow monthly, at intermediate or central level, the field application of the treatment programme.

3. Evaluation of the results of a treatment programme

   The basic method consists of assessing the status of cohorts of patients one year after the start of treatment, and of measuring according to the initial diagnosis (site of the disease and bacteriological status) the number of deaths, cures, transfers, chronic cases and defaulters.
   Evaluation of results can be permanent (routine) or periodical (or centralized) and retrospective or prospective.

   Permanent evaluation may be carried out retrospectively in all health areas where the register of reported cases is kept up-to-date, or, which is a harder and slower method, by analysis of patients' individual files.

   The simplest method is the study of the status one year after the start of treatment of a cohort of sputum positive pulmonary tuberculosis patients who were admitted over a given period.

In a more advanced stage it is possible to organize periodically, every five to seven years, prospective studies on treatment programme results in a national representative sample. For this purpose, a health unit's sample representative of all the country health units should be selected and 800 to 1600 registered pulmonary tuberculosis cases are followed up for a given period.

Clinical, bacteriological and radiological examinations concerning these patients at the start and at the end of treatment, should be assembled at central level. Pre-treatment sputum samples should also be collected and examined by microscopy, culture and sensitivity test at the central reference laboratory. Continuous information on evolution of patients during treatment should be reported to central level.

This national survey is more expensive and difficult to organize than the previous one; but it is more objective and precise. It gives valuable data to assess the results of the programme and eventually to introduce corrective modifications: changes in the organization of treatment or changes in the chemotherapy regimens.

J. HOW TO IMPLEMENT PROGRESSIVELY A STANDARDIZED CHEMOTHERAPY PROGRAMME IN A SITUATION OF ANARCHY

In many countries, the chemotherapy programme selected by the health authorities is not applied, either because it is unknown to the health personnel, or because the prescribing doctors refuse it, or because it is not applicable (lack of drugs or guidelines, inadequate basic health services). In such a situation chronic cases accumulate as the years pass, the level of bacterial resistance increases and doctors call more and more for expensive drugs that the community cannot provide.

1. How to recognize such a situation?

An evaluation survey in a few treatment centres having archives or registers will quickly identify this situation:

- more negative patients than positive patients are admitted to treatment
- among the smear positive pulmonary tuberculosis patients admitted to treatment, there are more "old" than "new" patients
- there are more patients who default before the end of their treatment than patients who complete their treatment
- the applied therapeutic regimens are not standardized.

2. How to correct this situation at national level?

Firstly, a national informative seminar should assemble all those responsible for the programme, those in charge of medical training at the University and the doctors most involved. A collective evaluation of the situation should be carried out by a group of a few persons in responsible positions (including at least one administrator from the health services, one clinician and one bacteriologist) and this should be followed by a communication of the most relevant information on modern chemotherapy of tuberculosis. At the end of the seminar, the general directives of the new programme should be agreed upon, and the most urgent corrective measures decided immediately. In a second step, the new technical directives are described in detail and circulated among all health personnel. The means for evaluation are set up through new organizational methods detailed in the technical directives. A supervisory team (or teams) visits the various health teams in each province in order to check on the application of the technical directives, to explain them whenever necessary, and to identify problems. During a third step, evaluation of the new policy of standardized chemotherapy can be carried out, 18 to 24 months after its application, either on the national level or in the more active

health units. Further seminars are then set up: either a second national seminar grouping all those who participated in the first seminar, or regional seminars with a view to disseminating the information as widely as possible or to more easily overcoming local resistance caused by the persistence of old habits. Regular evaluation seminars, held at all levels, make it possible to involve in evaluation tasks an ever-increasing number of health personnel, and to extend the measures of standardization and simplification of chemotherapy to the whole country.

3. How to correct a deficient situation at health centre level?

If it has been decided to implement, e.g. an 8-month standard regimen:

a) all the new cases registered after the issue of the new directives should be treated according to the new regimen.
b) all the old cases admitted to treatment for the last two years, or still under treatment, should be analysed individually and a decision taken for each of them.

For all old pulmonary cases, two sputum smears are requested:

- all those who have been treated for 12 months or more and have had two negative sputum smears are considered cured and their treatment is stopped

- those who have been treated for less than 12 months and who have smear negative sputum should follow the old standard regimen up to completion of the twelfth month.

- those who have smear positive sputum should be carefully assessed and the drugs they have taken identified. In general, they should follow the new standard regimen (and not a retreatment regimen) as they have in fact never had a treatment which was adequate in both quality and duration.

For extrapulmonary tuberculosis, clinical and possibly also radiological examination should be performed:

- those who have been treated for 12 months or more should be considered cured and treatment stopped

- those treated for less than 12 months should be treated with the old standard regimen until they have completed 12 months.

Once the standardization of the chemotherapy regimens has been enforced, it is necessary to ensure, through the described methods of management and supervision, that the directives are in fact respected; it is also necessary to point out to the health personnel concerned, using evaluation methods, that the efficiency of the services has actually improved (less work, less drug wastage, more cures, less defaulting).

K. HOW TO INTRODUCE NEW CHEMOTHERAPY REGIMENS

In those countries where standard chemotherapy regimens are being applied already but where they are inappropriate (i.e. 18-month regimens), or in cases where it is intended to introduce new standard regimens which differ in composition or duration, the movement towards change should involve an improvement in the entire treatment programme, in both technical and organizational aspects. The change is made progressively and implies the following:

1) A national survey should be conducted to evaluate the existing regimen, if possible on a national representative sample.

2) If, in the new regimen, there are drugs which have never been utilized on a large scale in the country, a survey should be organized, preferably in several regions, in order to test the acceptability and toxicity of the new regimens. This survey should cover small groups of 20-30 strictly supervised patients in each place. If the new regimens contain only well known drugs, it is possible to omit this survey.

3) Under the responsibility of a competent clinician, a controlled study should be organize to compare the old and the new regimens in two groups of patients chosen at random. These groups should be sufficiently large for the results to have a statistical significance.

4) A national seminar should be held to present the status of chemotherapy of tuberculosis throughout the world and the results of the acceptability survey and the controlled study to all personnel concerned in the application of the new regimens. This seminar would bring about general agreement as to the adjustment of technical chemotherapy directives.

5) The newly chosen regimens should be applied under routine conditions on a limited scale. The validity of the new technical directives should be tested.

6) The new regimens applied to the first 50 to 100 patients in each district should be evaluated one year after the end of treatment.

7) The evaluation of the results of the new regimens should be presented during a second national seminar. Adoption of the new technical directives should be discussed and a date should be set for the start of the new programme.

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BCG Vaccination[1]

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At the beginning of this century, several biologicals were used in attempts to prevent tuberculosis by developing a degree of resistance similar to that observed in previously infected persons. Calmette and Guérin observed changes in the characteristics of colonies in cultures contaminated with oxbile and used their findings to obtain an attenuated strain of *Mycobacterium bovis* (BCG). After 231 passages through media containing glycerin and oxbile, this BCG strain was unable to produce progressive lesions in experimental animals such as guinea pigs, rabbits, monkeys, and calves.

On May 21, 1921, Dr. Weil Hallé in Paris for the first time administered a vaccine to a child at high risk of acquiring tuberculosis. The child experienced no untoward reaction. Based on this and other clinical observations, the use of BCG vaccination quickly spread across Europe.

The vaccine was initially administered by mouth. Later, it was given by subcutaneous injection, which produced excessive local tissue destruction. Finally, it was given by the intradermal route.

The publications of Petroff in the United States and the disaster in Lübeck, Germany in 1930 generated more than 10 years of discussions on the safety of BCG and the possibility of virulent mutations of the strain. The episode in Lübeck, Germany, in which 72 children died, was due to a laboratory error, the contamination of the vaccine with a virulent strain (Kiel), which at the moment was thought to be fully attenuated. This strain produces a particular coloration in cultures, which allowed its identification as the cause of disease and deaths. However, by 1945, this method for preventing tuberculosis was well-established, based largely on clinical observations, individual experience, and a few uncontrolled studies on the relative risks in vaccinated and unvaccinated persons. As described by Guld (1), the studies of Heimbeck, in nurses in Oslo, and of school girls in Hyge, confirmed that vaccination conferred good protection against tuberculosis.

The principal controlled studies of the efficacy of BCG are reproduced in table 1 (2). The results show wide variation in protection, from 0 to 80%. Several hypotheses have been proposed to explain these differences. The most probable factors influencing the results are the quality of the vaccine, and partial protection due to infection with nontuberculous ("atypical") mycobacteria. In the Aronson trial (9), a vaccine produced in poor culture medium resulted in diminished tuberculin conversion rates (16 versus 46%) and decreased protection during a 5-year period (53 versus 80% in the total population). Some of the strains produced by the Tice Laboratory around 1950 showed low activity in animal experiments, which is compatible with low immunogenicity.

The route of administration of BCG vaccine is also important. Only intradermal injection with a syringe and needle permits adequate measurement of an individual dose. A multipuncture technique was used in Georgia (4), Alabama (3), and Illinois (1).

The discovery of a high prevalence of low-grade tuberculin sensitivity in humid tropical and subtropical areas, interpreted as cross reactions due to the sensitization to nontuberculous mycobacteria, and the animal experiments showing that these infections confer partial protection against *Mycobacterium tuberculosis* (3) led to the hypothesis that atypical infection diminishes or masks the effect of BCG by providing partial immunity. Although there is general agreement that this effect is important, it alone cannot completely explain the lack of protection found in some studies.

A new study was started in Chingleput, South India in 1968 in an attempt to avoid the methodologic errors that might have affected previous trials (4). Two doses of two different strains of BCG were compared with a placebo. The area was known to have a high prevalence of nontuberculous mycobacterial infection, and purified protein derivative (PPD)-B was used in addition to PPD-S to distinguish infections due to these mycobacteria. Subjects of all ages were included, with a total study population near 250,000 persons. This was the first trial in which the vaccines used were freeze-dried and stored. In previous studies, the BCG strains were lost or might have undergone changes caused by permanent transfers in culture media.

The findings of this trial, which was sponsored by the World Health Organization (WHO), the Indian Council of Medical Research, and the U.S. Public Health Service, were disappointing: (*1*) The vaccinated and unvaccinated groups previously classified as not infected had similar incidences of disease; no protective effect of BCG was apparent. (*2*) The unvaccinated group had a very low incidence of active tuberculosis after infection, whereas the previously infected population produced large numbers of bacillary cases, maintaining a high annual risk of tuberculosis.

The trial tried to compensate for the lack of bacteriologic data in previous trials and the possibility of interference from tuberculosis control programs. Therefore, the study was oriented toward bacteriologically proved pulmonary tuberculosis in adults, and the area selected was almost completely lacking in resources for diagnosis, especially for primary tuberculosis in children. No data are available from the study to evaluate protection in children, which is the current target group for world vaccination. The results, then, cannot be extrapolated to current vaccination practices.

Very little disease was observed in the period immediately after infection. It is not clear whether this was due to lack of diagnostic facilities, or to real differences between the epidemiologic model observed in India in previous

[1] From the Pan American Health Organization, Washington, D.C.

TABLE 1

RESULTS OF 8 CONTROLLED TRIALS OF BCG VACCINATION AGAINST TUBERCULOSIS*

Population group and reference	Period of intake and age range	Criterion of eligibility for vaccination	Source of vaccine	Duration of follow-up (years)	Vaccination group	No. of subjects	Cases of tuberculosis		Protective efficacy (%)
							No.	Rate†	
North American Indians, 8 tribes (9)	1935-38 0-20 yr	Negative to 0.005 mg PPD-Seibert (250 TU)	Henry Philipps Institute, Philadelphia	9-11	Unvaccinated BCG	1,457 1,551	238 64	1,563 320	80‖
Chicago infants, high-risk areas (3)	1937-48 under 3 months	(No initial tuberculin testing)	Tice Laboratory, Chicago§	12-23	Unvaccinated BCG	1,665 1,716	65 17	223‖ 57‖	75
Georgia, schoolchildren (14)	1947 6-17 yr	Under 5 mm to 0.002 mg RT 18 (100 TU)	Tice Laboratory, Chicago§	20	Unvaccinated BCG	2,341 2,498	3 5	11 17	None
Illinois, school for the mentally retarded (11)	1947-48 Adolescents and young adults	Negative to 1/1000 and 1/100 OT	Tice Laboratory, Chicago§	12	Unvaccinated BCG	494 531	8 12	— —	None
Puerto Rico, general population (10)	1949-51 1-18 yr	Under 6 mm to 0.0002 mg RT 19-20-21 (10 TU)	State Department of Health, New York	5½-7½ (Mean: 6.3)	Unvaccinated BCG	27,338 50,634	73 93	43 30	31
Georgia & Alabama, general population (13)	1950 5 yr and over	Under 5 mm to 0.0001 mg RT 19-20-21	Tice Laboratory, Chicago§	14	Unvaccinated BCG	17,854 16,913	32 26	13 11	14¶
Great Britain, urban populations (12)	1950-52 14-15½ yr	Under 5 mm to 0.1 ml 1/100 Old Tuberculin (100 TU)	Statens Seruminstitut, Copenhagen	15	Unvaccinated BCG	12,699 13,598	240 56	128 28	78
South India, rural population (15)	1950-55 All ages	Under 5 mm to 5 TU RT 19-20-21	BCG Laboratory, Madras	9-14 (Mean: 12.3)	Unvaccinated BCG	5,808 5,069	46 28	89 61	31

* Reproduced from ten Dam, *et al.* (2).
† Annual rate per 100,000 population, usually allowing for losses from observation.
‡ The protective efficacy against death from tuberculosis was 82 % for a period of 18-20 years.
§ This laboratory has produced a number of strains at different times and it is not known whether the strains used in these four trials were the same or not.
‖ Assuming a mean observation period of 17.5 yr.
¶ Not significant.

trials and that of western countries. The relation between incidence of disease in previously infected and in recently infected persons was 1:16, whereas it was 1:1 in the British study (12). The sex distribution was also greatly changed, with 3 male cases to 1 female case. Comparing the age distribution of the cases in the total population with the distribution in South American countries having similar risks of infection (nearly 3% per yr), the absence in India of incidence peaks in young children and in young adults is striking. Only the former may be due to lack of diagnosis. In contrast, incidence increases logarithmically with age to more than 1,000 cases per 100,000 persons.

These observations could be explained by a long delay in tuberculous breakdown after primary infection (in which case any effect of BCG would be observed much later, as in the study of Frimodt-Møller in South India [6]) or by repeated infections (in which case the vaccine would not show any protection).

Two meetings on this subject were recently convened by WHO. Participants of the first one, in New Delhi (5), recognized that there were no major methodologic errors that could have produced the observed results. They recommended a series of research proposals designed to produce results that could explain the findings. Participants of the second meeting, in Geneva (6), analyzed the results and their relevance to current vaccination policies. They recommended maintaining the current BCG policy in countries with a high risk of infection with tuberculosis: administer BCG vaccine as early in life as possible.

The main reason for this recommendation was that BCG has shown a protective effect in all studies in young children (7), and the study in India did not produce any contradictory evidence. In several European countries where BCG vaccination was suspended

TABLE 2

BCG VACCINATION COVERAGE PER 100 POPULATION (PROVISIONAL DATA). REGION OF THE AMERICAS, 1980*

Country	Est. pop. under 1 year of age	BCG
Argentina	674,000	64
Bahamas	5,400	71
Barbados	4,200	—
Bolivia	103,380	49
Brazil	3,582,640	58
Canada	372,000	—
Chile	243,000	99
Colombia	765,000	40
Costa Rica	72,000	79
Cuba	136,900	99
Dominica	2,600	...
Dominican Rep.	184,650	17
Ecuador	327,950	74
El Salvador	188,033	56
Grenada	2,700	...
Guatemala	246,994	43
Guyana	23,000	60
Haiti	216,013	22
Honduras	164,543	26
Jamaica	58,500	...
Mexico	2,848,000	40
Nicaragua	114,685	33
Panama	53,853	68
Paraguay	105,461	31
Peru	690,000	48
Saint Lucia	4,000	...
St. Vincent and the Grenadines	3,300	...
Suriname	14,500	...
Trinidad and Tobago	26,300	—
U.S.A.	3,276,000	—
Uruguay	53,386	96
Venezuela	506,441	66

Definition of abbreviations: — = No routine vaccination under 1 yr old; ... = Data unavailable.
* Source: PAHO/WHO, Expanded Program of Immunization, 1981.

because of the low risk of infection, childhood tuberculosis has recently reappeared within the expected frequency.

The objective of using BCG in control programs is to prevent childhood tuberculosis, especially the more serious forms such as meningitis. It has been recognized for several years that, even if BCG has a protection of 80% in vaccinated persons and a high coverage is achieved, the effect on the chain of transmission of infection is very low (8). The decisions on vaccination policy should be based on the risk of infection (and disease in children, as shown in India), as well as economic and sociologic considerations, such as acceptance of local reactions (9).

The present WHO policy in countries with a high risk of infection is BCG vaccination of newborns when feasible, or of children less than 1 year of age simultaneously with other vaccines, as recommended by the WHO Expanded Program on Immunization (table 2). Revaccination is usually administered in the first year of primary school. Freeze-dried products are preferred, and the most commonly used strains are Pasteur 1173P2, Copenhagen 1331, Glaxo, Tokyo 172, and Moreau (Brazil, Cuba). In routine control vaccination programs, direct vaccination without previous tuberculin test is preferred for its operational advantages.

Vaccination does not have increased risk in previously infected persons, and the need for tuberculin testing and reading is avoided, thus improving the coverage and reducing the cost. Vaccination induces skin sensitivity to the tuberculin test, of a somewhat lower degree than natural infection and waning faster than induced protection. Therefore, the tuberculin test loses its value (except for very strong reactions) in vaccinated individuals, and cannot be used as an indicator for revaccination.

A comprehensive analysis of vaccination practices and undesirable reactions has been compiled by Lotte and Wasz-Hockert for the International Union Against Tuberculosis (10). Serious general reactions, including deaths, are very rare in world literature, and BCG is one of the safest vaccines. Most local and regional undesirable reactions are of little consequence and slowly evolve the resolution and cure, usually without treatment. Oversized ulcers or scars are generally caused by too deep injections, less frequently by excessive dose. In just 25 years (from 1949 to 1974), 187 countries vaccinated almost 1.4 billion persons with BCG. This effort and investment justifies the expenditures in BCG research.

At present, BCG research is focused on two topics: protection of children who are contacts of bacillary patients, in attempts to obtain results in short periods of time, and the immunologic mechanisms of disease and protection. Information obtained from the latter may prove useful not only in tuberculosis, but also in leprosy. The vaccines being tried are mixtures of BCG with killed leprosy bacilli, and the immunologic mechanism might be similar in both diseases.

Analysis of other areas of the world with epidemiologic characteristics similar to those of South India (prevalence of nontuberculous mycobacteria, low-virulence variants of *M. tuberculosis*, and an epidemiologic model different from the classic one) is also a priority for developing regional and national policies on BCG vaccination.

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Efficacy of Infant BCG Immunization

BCG immunization is widely practiced within the Expanded Program on Immunization (EPI). However, information on the efficacy of BCG in preventing childhood tuberculosis is scarce, and the policy has been challenged by the results of a large-scale controlled trial in South India. Recent studies, which have been designed to avoid the pitfalls of earlier trials, now confirm that BCG immunization of newborns and young children provides a significant level of protection against tuberculosis in childhood, especially against tuberculous meningitis where the protective effect may be as high as 95%. WHO continues to recommend BCG immunization for all newborns or young children in high-risk countries or areas.

In accordance with the recommendations of a WHO Study Group, the Organization initiated a program of evaluating BCG immunization of newborns and young children in developing countries using two techniques. The first is the case-control study, in which the immunization coverage is determined in patients and in matching controls so that the relative risk of the unimmunized child contracting tuberculosis can be estimated. The second is the contact study, in which the relative risk is determined from the incidence of tuberculosis in actively followed-up child contacts of newly detected patients with infectious tuberculosis.

Both techniques use stratification to deal with the problem of comparability, an issue which has frequently evoked justifiable criticism of studies other than controlled trials. In case-control studies the controls are matched with the cases for characteristics which could influence the incidence or the immunization coverage, such as sex, age, and socioeconomic status. In contact studies these characteristics are recorded, and stratified analysis is applied if both the incidence and the coverage are found to vary from stratum to stratum.

Since both techniques make it possible to include many cases at low cost and in a short period of time, they are far more efficient than controlled trials, provided that the BCG immunization coverage is not extremely high or low. The techniques can be used to advantage where an immunization program is already established in a country, and therefore controlled trials might not be justified ethically. Five such studies have been completed with support from WHO.

WHO-supported studies

In a case-control study in São Paulo, Brazil, 73 cases of tuberculous meningitis were traced that occurred in 1981-1983 in children up to 4 years of age admitted to two hospitals. For each case, seven neighborhood controls and one hospital control were matched for age, sex, area and socioeconomic status. Fifty-two percent of cases had previously been immunized, compared with 90% of controls. The estimated protective effect was 90% or 87%, depending on whether the neighborhood or hospital controls were considered. Of the 73 hospital cases, 37 had died from meningitis, 19 had serious, and 4 mild neurological sequelae, 2 died later, and the remaining 11 appeared healthy. Therefore, as regards tuberculous meningitis alone, over 400 deaths and over 200 cases of serious sequelae have been prevented so far in the population in which the cases occurred.

A contact study carried out in Bangkok, Thailand in 1981-1984, included 1,507 child contacts, up to 5 years of age, of newly detected smear-positive cases of pulmonary tuberculosis. Of the 218 children diagnosed as having tuberculosis (mostly by X-ray), 158 were from the group of 1,253 who had been immunized and 60 from the group of 253 who were unimmunized. Detailed analysis showed a protective effect of 53% against all forms of the disease, indicating that in the study population 185 cases were probably prevented by the immunization. The protective effect was over 60% against multiple lesions and extrapulmonary tuberculosis, but lower for other forms.

Another contact study was carried out in Lomé, Togo in 1983-1985 in 1,421 child contacts up to 6 years of age, among whom 175 were found to suffer from tuberculosis: 62 cases among the 875 immunized, and 113 among the 546 non-immunized. The protective effect was over 80% for the more extensive and serious types of tuberculosis, and less than 50% for milder forms. The protective effect appeared to be reduced in children under 1 year and over 4 years of age.

In Rangoon, Burma, a hospital-based case-control study was carried out in children up to 5 years of age in 1982-1985 comprising 311 cases, each with 5 controls matched for age, sex and township. The immunization coverage was 52% among the cases and 64% among the controls. The protective effect was 39%, with 95% confidence limits of 22% and 52%. Protection was only 20% among 89 cases clasified as primary complex, and apparently there was no protection against abdominal and bone tuberculosis. Protection was about 50% for tuberculous pneumonia, lymphadenitis and meningitis, and 80% for disseminated tuberculosis. Protection decreased with increasing age.

A similar study carried out in Buenos Aires, Argentina, comprised 175 cases up to 5 years of age and 875 controls matched for age, sex, socioeconomic status and district.

Immunization coverage among the cases was 29% and among the controls 59%. Stratified analysis shows an overall protective effect of 74% (with 95% confidence limits of 82% and 62%). In this study, protection apparently increased with age from around 50% in children under 1, to more than 80% in children of 3 years of age and over.

Other retrospective studies

A few retrospective studies have been reported in industrialized countries that refer to the efficacy of BCG immunization in newborns. The incidence of tuberculosis among unimmunized children was found to be four times higher than that of immunized children in a study carried out in Manchester, United Kingdom, where BCG immunization was offered to newborns. A study from 1956 to 1979 in Israel showed that BCG immunization at birth had an overall protective effect of 38% in children 0-12 years, of 24% for pulmonary and 64% for extra-pulmonary disease. In Japan in 1979, 30 cases of tuberculous meningitis were reported in children aged 0-4 years. Only 3 of the children had been immunized, whereas the estimated coverage in this group was 69%. The data are compatible with a protective effect against meningitis of about 95%. In Sweden, BCG immunization of the newborn was discontinued in 1975. The incidence of the disease in children born in 1969-1974 was compared with the incidence in children born in 1975-1980. For pulmonary, miliary and meningeal tuberculosis there were 5 and 23 cases in the respective periods and for lymphadenopathy 1 and 13 cases. Furthermore, 78 cases of mycobacteriosis (mainly with *M. avium-intracellulare*) occurred after BCG immunization was discontinued, whereas only 1 such case had been observed in the previous period.

Conclusion

Although the results appear much less ambiguous than those of the controlled trials, estimates of protection still vary widely. Such variations, however, occur within studies as well as between them. The estimated immunization efficacy may have been reduced in several ways. Probably protection against the more serious forms is likely to have been estimated accurately, as serious forms of tuberculosis stand out and are easier to diagnose than mild ones. In milder forms, evidence limited to hilar lymphadenopathy on X-ray may merely be indicative of recent infection. If these are counted as positive cases, "mild cases" will be over-estimated and will distort the data so that the protective effect of immunization appears to be lower.

A cause of diminished protection may lie in re-infection. Young children almost always contract infection through intrafamilial transmission, associated with an increased risk of disease, probably because the infectious load is larger or infection occurs repeatedly. In the latter case BCG may not show protection since the first infection will have induced immunity, whether or not BCG immunization was carried out.

Finally, the reduced protection observed in the youngest children may be explained by the possibility that the index case already existed (undetected) when the child was born so that infection may have occurred before BCG had induced immunity.

Although the foregoing factors may explain, to some extent, the variations in protection, a more important issue is probably the quality of the immunizations. Although it is not possible to tell whether a particular vaccine is more effective than another, there seems to be ample room for technical improvement in vaccine administration. Tuberculin testing carried out in the contact studies revealed that even those who received BCG vaccine often showed little or no skin reaction, suggesting that immunization had induced very little lasting sensitivity. Notwithstanding the fact that the response in the newborn is known to be reduced, it appears that the dose of vaccine administered is sometimes too small.

In view of the importance of intra-familial transmission of childhood tuberculosis, WHO recommends that in high-risk countries and areas, immunization of infants should continue to be carried out, within the EPI, as early in life as possible. Although the response to BCG may be reduced at this age, studies have shown that there is significant protection provided in childhood by BCG immunization against all forms of tuberculosis, but especially for the more serious forms, such as tuberculous meningitis.

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